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(54) Title: NUCLEIC ACID LIGANDS OF TISSUE TARGET

(57) Abstract

This invention discloses high-affinity oligonucleotide ligands to complex tissue targets, specifically nucleic acid ligands having the ability to bind to complex tissue targets, and the methods for obtaining such ligands. Tissue targets comprise cells, subcellular components, aggregates or cells, collections of cells, and higher ordered structures. Specifically, nucleic acid ligands to peripheral blood mononuclear cells (PBMC), fibrin clots, and carotid arteries are described.

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NUCLEIC ACID LIGANDS OF TISSUE TARGET

RELATED APPLICATIONS

FIELD OF THE INVENTION

Described herein are methods for identifying and preparing nucleic acid ligands to tissues. Tissues are described herein as a collection of macromolecules in a heterogeneous environment. According to this definition, tissues encompass a single cell type, a collection of cell types, an aggregate of cells or an aggregate of macromolecules. The method utilized herein for identifying such nucleic acid ligands is called SELEX, an acronym for Systematic Evolution of Ligands by EXponential enrichment. Specifically disclosed herein are high-affinity nucleic acid ligands which bind to various tissues.

BACKGROUND OF THE INVENTION

A method for the in *vitro* evolution of nucleic acid molecules with highly specific binding to target molecules has been developed. This method, Systematic Evolution of Ligands by EXponential enrichment, termed SELEX, is described in United States Patent Application Serial No. 07/536,428, entitled "Systematic Evolution of Ligands by Exponential Enrichment", now abandoned, United States Patent Application Serial No. 07/714,131, filed June 10, 1991, entitled "Nucleic Acid Ligands", United States Patent Application Serial No. 07/931,473, filed August 17, 1992, entitled "Nucleic Acid Ligands", now United States Patent No. 5,270,163 (see also PCT/US91/04078), each of which is herein specifically incorporated by reference. Each of these applications, collectively referred to

herein as the SELEX Patent Applications, describes a fundamentally novel method for making a nucleic acid ligand to any desired target molecule.

The SELEX method involves selection from a mixture of candidate oligonucleotides and step-wise iterations of binding, partitioning and amplification, using the same general selection scheme, to achieve virtually any desired criterion of binding affinity and selectivity. Starting from a mixture of nucleic acids, preferably comprising a segment of randomized sequence, the SELEX method includes steps of contacting the mixture with the target under conditions favorable for binding, partitioning unbound nucleic acids from those nucleic acids which have bound specifically to target molecules, dissociating the nucleic acid-target complexes, amplifying the nucleic acids dissociated from the nucleic acid-target complexes to yield a ligand-enriched mixture of nucleic acids, then reiterating the steps of binding, partitioning, dissociating and amplifying through as many cycles as desired to yield highly specific, high affinity nucleic acid ligands to the target molecule.

The basic SELEX method has been modified to achieve a number of specific objectives. For example, United States Patent Application Serial No. 07/960,093, filed October 14, 1992, entitled "Method for Selecting Nucleic Acids on the Basis of Structure", describes the use of SELEX in conjunction with gel electrophoresis to select nucleic acid molecules with specific structural characteristics, such as bent DNA. United States Patent Application Serial No. 08/123,935, filed September 17, 1993, entitled "Photoselection of Nucleic Acid Ligands" describes a SELEX based method for selecting nucleic acid ligands containing photoreactive groups capable of binding and/or photocrosslinking to and/or photoinactivating a target molecule. United States Patent Application Serial No. 08/134,028, filed October 7, 1993, entitled "High-Affinity Nucleic Acid Ligands That Discriminate Between Theophylline and Caffeine", describes a method for identifying highly specific nucleic acid ligands able to discriminate between closely related molecules, termed Counter-SELEX. United States Patent Application Serial No. 08/143,564, filed October 25, 1993, entitled "Systematic Evolution of Ligands by EXponential Enrichment: Solution SELEX", describes a

SELEX-based method which achieves highly efficient partitioning between oligonucleotides having high and low affinity for a target molecule. United States Patent Application Serial No. 07/964,624, filed October 21, 1992, entitled "Methods of Producing Nucleic Acid Ligands" describes methods for obtaining improved nucleic acid ligands after SELEX has been performed. United States Patent Application Serial No. 08/400,440, filed March 8, 1995, entitled "Systematic Evolution of Ligands by EXponential Enrichment: Chemi-SELEX", describes methods for covalently linking a ligand to its target.

The SELEX method encompasses the identification of high-affinity nucleic acid ligands containing modified nucleotides conferring improved characteristics on the ligand, such as improved *in vivo* stability or improved delivery characteristics. Examples of such modifications include chemical substitutions at the ribose and/or phosphate and/or base positions. SELEX-identified nucleic acid ligands containing modified nucleotides are described in United States Patent Application Serial No. 08/117,991, filed September 8, 1993, entitled "High Affinity Nucleic Acid Ligands Containing Modified Nucleotides", that describes oligonucleotides containing nucleotide derivatives chemically modified at the 5- and 2'-positions of pyrimidines. United States Patent Application Serial No. 08/134,028, *supra*, describes highly specific nucleic acid ligands containing one or more nucleotides modified with 2'-amino (2'-NH_2), 2'-fluoro (2'-F), and/or 2'-O-methyl (2'-OMe). United States Patent Application Serial No. 08/264,029, filed June 22, 1994, entitled "Novel Method of Preparation of 2' Modified Pyrimidine by Intramolecular Nucleophilic Displacement", describes oligonucleotides containing various 2'-modified pyrimidines.

The SELEX method encompasses combining selected oligonucleotides with other selected oligonucleotides and non-oligonucleotide functional units as described in United States Patent Application Serial No. 08/284,063, filed August 2, 1994, entitled "Systematic Evolution of Ligands by Exponential Enrichment: Chimeric SELEX" and United States Patent Application Serial No. 08/234,997, filed April 28, 1994, entitled "Systematic Evolution of Ligands by Exponential

Enrichment: Blended SELEX", respectively. These applications allow the combination of the broad array of shapes and other properties, and the efficient amplification and replication properties, of oligonucleotides with the desirable properties of other molecules. Each of the above described patent applications which describe modifications of the basic SELEX procedure are specifically incorporated by reference herein in their entirety.

Without question, the SELEX process is very powerful. However, to date the process has been successfully demonstrated primarily with pure, simple targets, such as proteins or small molecules. The present invention provides the first demonstration that complex targets are also compatible with the SELEX process.

It is desirable to be able to obtain nucleic acid ligands to complex tissue targets for various reasons. First, tissue SELEX can be useful to obtain nucleic acid ligands when a distinct target is unknown but a general mode of action of the desired ligand is suggested. Second, tissue SELEX can be useful when nucleic acid ligands are desired based on functional results. Third, it can be desirable to obtain nucleic acid ligands to a complex tissue target when it is unclear which single target would be effective. It is also useful to obtain nucleic acid ligands to a complex tissue target if the purified target is unavailable or unstable in its purified form (i.e., a membrane protein).

BRIEF SUMMARY OF THE INVENTION

The present invention includes methods of identifying and producing nucleic acid ligands to complex targets such as tissues and the nucleic acid ligands so identified and produced. More particularly, nucleic acid ligands are provided that are capable of binding specifically to tissues which are macromolecules in a heterogeneous environment, such as whole cells or substructures thereof, aggregates of cells, collections of cells, aggregates of macromolecules and the like.

Further included in this invention is a method of identifying nucleic acid ligands to tissues comprising the steps of (a) preparing a candidate mixture of

nucleic acids, (b) partitioning between members of said candidate mixture on the basis of affinity to tissue, and (c) amplifying the selected molecules to yield a mixture of nucleic acids enriched for nucleic acid sequences with a relatively higher affinity for binding to tissue. Also included are nucleic acid ligands identified according to such method.

Another embodiment of the invention includes methods wherein a negative selection is performed in order to perfect the discrimination between subtle differences of similar tissue types. In this embodiment, the resulting ligands are specific not only for a particular tissue type, but can discriminate between subtly different tissues of the same type. For example, this method can discriminate between normal and abnormal tissue types, between induced and uninduced tissue types, etc.

In another embodiment of the invention, a method is provided for identifying previously unknown or uncharacterized epitopes which are components of a larger unknown macromolecule on the tissue target. The ligands that are evolved by the present invention are capable of binding to previously unknown epitopes and the macromolecule which comprises the unknown epitope can then be identifed by standard methods. For example, ligands can be evolved to a previously unknown protein found in the context of a complex tissue target. The ligand of the invention can be used to purify the protein away from the tissue target by standard protein purification and identification methods. These standard methods include affinity purification, microsequencing and cDNA databank searches. In this aspect, the newly identified epitopes which are components of a larger unknown macromolecule, such as new or previously uncharacterized proteins, are provided by the invention. These new epitopes and the macromolecules of which they are a component will be useful as diagnostic and therapeutic agents as well as the ligands that helped identify them.

More specifically, the present invention includes nucleic acid ligands to peripheral blood mononuclear cells (PBMC), clots and restenotic arterial cells, including those ligands shown in Tables 2, 5, and 8, respectively. Also included are nucleic acid ligands to the above-described tissues that are substantially

homologous to any of the given ligands and that have substantially the same ability to bind the above-described tissues. Further included in this invention are nucleic acid ligands to the above-described tissues that have substantially the same structural form as the ligands presented herein.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows a schematic representation used in the carotid artery SELEX procedures.

DETAILED DESCRIPTION OF THE INVENTION

This application describes nucleic acid ligands to complex tissue targets identified generally according to the method known as SELEX. As stated earlier, the SELEX technology is described in detail, and incorporated herein by reference, in the SELEX Patent Applications. This method, referred to as Tissue SELEX, incorporates complex targets in contrast to the more simple targets previously used in the SELEX process. Certain terms used to describe the invention herein are defined as follows:

"SELEX" methodology refers to the combination of selection of nucleic acid ligands which interact with a target in a desirable manner, for example binding to a protein, with amplification of those selected nucleic acids as described in detail above and in the SELEX Patent Applications. Iterative cycling of the selection/amplification steps allows selection of one or a small number of nucleic acids which interact most strongly with the target from a pool which contains a very large number of nucleic acids. Cycling of the selection/amplification procedure is continued until a selected goal is achieved.

"Tissue SELEX" methodology applies the SELEX methodology to tissue targets. Tissue SELEX has several advantages. First, using Tissue SELEX one can obtain ligands to specific cell types in the absence of a defined understanding of the involved epitope. The epitope against which a ligand is evolved in usually a substructural component of a larger macromolecule The ligands found by this method could also be useful in identifying new proteins or other new

macromolecules on the tissue target. The new proteins or other new macromolecules which comprise a newly identified epitope can be purified and characterized using standard procedures. Second, ligands can be obtained to defined epitopes or macromolecules in the context of their physiologic cellular or membrane environment. Third, it is possible to obtain ligands to tissues in a functionally altered phenotype, e.g., activated, migrating, etc. The ligands and the new macromolecules containing the ligand epitopes identified by this process may be useful as diagnostics or therapeutics.

Tissue SELEX is a powerful methodology which allows one to identify nucleic acid ligands that can mediate many different cell behaviors, such as apoptosis, anergy, differentiation, proliferation, etc., without prior knowledge of the identity of the specific tissue targets that control these changes. The sensitivity of the SELEX process may lead to the generation of oligonucleotides that recognize potentially every different epitope on the complex tissue target. Larger numbers of different sequence motifs are expected using the tissue SELEX process, as compared with simple-target SELEX, since it is believed that different motifs will recognize distinct epitopes on the complex tissue target. Some epitopes may lie within the same protein, but many will be directed to various proteins or other molecules on the tissue. Tissue SELEX can be done *in vivo* or *in vitro*.

In one embodiment, a negative selection process (termed counter-SELEX) is employed to enhance the possibility that the ligands derived by tissue SELEX have precise specificity and affinity. In this embodiment, ligands are selected for a specific tissue and then a negative selection is done against a related tissue which does not have certain characteristics for which the ligand is desired. The negative selection can be done against a similar cell line or cell type, different cells, normal tissue, plasma or blood, a non-specific antibody or other available ligand. An example of this negative selection would be to first select using a tumor cell target (such as a malignant melanoma) and then counterselect the resulting nucleic acids against a similar cell type which is not tumorogenic (such as normal human melanocytes). Ligands that interact with both normal and

neoplastic tissue will be removed by this negative selection and only those nucleic acid ligands that specifically bind the tumor cells will be identified (or retained). The resulting nucleic acid ligand would be specific for tumors. This technique will provide the ability to identify nucleic acid ligands that can discriminate between two closely related targets, i.e., between a cancerous cell and an untransformed cell of the same tissue type. The negative selection can also be done *in vivo*. Using this method one can not only generate ligands to specific targets on complex tissue surfaces, but also be able to recognize the differences between normal and abnormal tissue of a particular type.

"SELEX Target" or "Target" refers to any compound upon which a nucleic acid can act in a predetermined desirable manner. A SELEX target molecule can be a protein, peptide, nucleic acid, carbohydrate, lipid, polysaccharide, glycoprotein, hormone, receptor, antigen, antibody, virus, pathogen, toxic substance, substrate, metabolite, transition state analog, cofactor, inhibitor, drug, dye, nutrient, growth factor, cell, tissue, etc., without limitation. Virtually any chemical or biological effector would be a suitable SELEX target. Molecules of any size can serve as SELEX targets. A target can also be modified in certain ways to enhance the likelihood of an interaction between the target and the nucleic acid.

"Tissue target" or "Tissue" refers to a certain subset of the SELEX targets described above. According to this definition, tissues are macromolecules in a heterogeneous environment. As used herein, tissue refers to a single cell type, a collection of cell types, an aggregate of cells, or an aggregate of macromolecules. This differs from simpler SELEX targets which are typically isolated soluble molecules, such as proteins. In the preferred embodiment, tissues are insoluble macromolecules which are orders of magnitude larger than simpler SELEX targets. Tissues are complex targets made up of numerous macromolecules, each macromolecule having numerous potential epitopes. The different macromolecules which comprise the numerous epitopes can be proteins, lipids, carbohydrates, etc., or combinations thereof. Tissues are generally a physical array of macromolecules that can be either fluid or rigid, both in terms of structure

and composition. Extracellular matrix is an example of a more rigid tissue, both structurally and compositionally, while a membrane bilayer is more fluid in structure and composition. Tissues are generally not soluble and remain in solid phase, and thus partitioning can be accomplished relatively easily. Tissue includes, but is not limited to, an aggregate of cells usually of a particular kind together with their intercellular substance that form one of the structural materials commonly used to denote the general cellular fabric of a given organ, e.g., kidney tissue, brain tissue. The four general classes of tissues are epithelial tissue, connective tissue, nerve tissue, and muscle tissue.

Examples of tissues which fall within this definition include, but are not limited to, heterogeneous aggregates of macromolecules such as fibrin clots which are acellular; homogeneous or heterogeneous aggregates of cells; higher ordered structures containing cells which have a specific function, such as organs, tumors, lymph nodes, arteries, etc.; and individual cells. Tissues or cells can be in their natural environment, isolated, or in tissue culture. The tissue can be intact or modified. The modification can include numerous changes such as transformation, transfection, activation, and substructure isolation, e.g., cell membranes, cell nuclei, cell organelles, etc.

Sources of the tissue, cell or subcellular structures can be obtained from prokaryotes as well as eukaryotes. This includes human, animal, plant, bacterial, fungal and viral structures.

"Nucleic acid" means either DNA, RNA, single-stranded or double-stranded and any chemical modifications thereof. Modifications include, but are not limited to, those which provide other chemical groups that incorporate additional charge, polarizability, hydrogen bonding, electrostatic interaction, and fluxionality to the individual nucleic acid bases or to the nucleic acid as a whole. Such modifications include, but are not limited to, modified bases such as 2'-position sugar modifications, 5-position pyrimidine modifications, 8-position purine modifications, modifications at cytosine exocyclic amines, substitution of 5-bromo-uracil; backbone modifications, methylations, unusual base-pairing combinations such as the isobases isocytidine and isoguanidine and the like.

Modifications can also include 3' and 5' modifications such as capping. Modifications that occur after each round of amplification are also compatible with this invention. Post-amplification modifications can be reversibly or irreversibly added after each round of amplification. Virtually any modification of the nucleic acid is contemplated by this invention.

"Nucleic acid test mixture" or "nucleic acid candidate mixture" is a mixture of nucleic acids of differing, randomized sequence. The source of a "nucleic acid test mixture" can be from naturally-occurring nucleic acids or fragments thereof, chemically synthesized nucleic acids, enzymatically synthesized nucleic acids or nucleic acids made by a combination of the foregoing techniques. In a preferred embodiment, each nucleic acid has fixed sequences surrounding a randomized region to facilitate the amplification process. The length of the randomized section of the nucleic acid is generally between 8 and 250 nucleotides, preferably between 8 and 60 nucleotides.

"Nucleic acid ligand" is a nucleic acid which has been isolated from the nucleic acid candidate mixture that acts on a target in a desirable manner. Examples of actions on a target in a desirable manner include, but are not limited to binding of the target, catalytically changing the target, reacting with the target in a way which modifies/alters the target or the functional activity of the target, covalently attaching to the target as in a suicide inhibitor, factilitating the reaction between the target and another molecule. In most, but not all, instances this desirable manner is binding to the target. In the most preferred embodiment, a nucleic acid ligand is a non-naturally occurring nucleic acid ligand having a specific binding affinity for a tissue target molecule, such target molecule being a three dimensional chemical structure other than a polynucleotide that binds to said nucleic acid ligand through a mechanism which predominantly depends on Watson/Crick base pairing or triple helix binding, wherein said nucleic acid ligand is not a nucleic acid having the known physiological function of being bound by the target molecule. Nucleic acid ligand includes nucleic acid sequences that are substantially homologous to the nucleic acid ligands actually isolated by the Tissue SELEX procedures. By substantially homologous it is meant a degree of

primary sequence homology in excess of 70%, most preferably in excess of 80%. In the past it has been shown that the sequence homologies of various nucleic acid ligands to a specific target shows that sequences with little or no primary homology may have substantially the same ability to bind the target. For these reasons, this invention also includes nucleic acid ligands that have substantially the same ability to bind a target as the nucleic acid ligands identified by the Tissue SELEX process. Substantially the same ability to bind a target means that the affinity is within a few orders of magnitude of the affinity of the ligands described herein. It is well within the skill of those of ordinary skill in the art to determine whether a given sequence -- substantially homologous to those specifically described herein -- has substantially the same ability to bind a tissue target.

"Partitioning" means any process for separating nucleic acid ligands from the remainder of the unreacted nucleic acid candidate mixture. Partitioning can be accomplished by various methods known in the art. Filter binding, affinity chromatography, liquid-liquid partitioning, filtration, gel shift, density gradient centrifugation are all examples of suitable partitioning methods. Equilibrium partitioning methods can also be used as described in detail below. Since the tissue targets of the present invention are non-soluble, there are numerous simple partitioning methods which are well suited to this invention. The simple partitioning methods include any method for separating a solid from a liquid, such as, centrifugation with and without oils, membrane separations and simply washing the insoluble tissue target. The ligands can also be specifically eluted from the target with a specific antibody or ligand. The choice of partitioning method will depend on properties of the target and the nucleic acid and can be made according to principles and properties known to those of ordinary skill in the art.

"Amplifying" means any process or combination of process steps that increases the amount or number of copies of a molecule or class of molecules. In preferred embodiments, amplification occurs after members of the test mixture have been partitioned, and it is the facilitating nucleic acid associated with a desirable product that is amplified. For example, amplifying RNA molecules can

be carried out by a sequence of three reactions: making cDNA copies of selected RNAs, using the polymerase chain reaction to increase the copy number of each cDNA, and transcribing the cDNA copies to obtain RNA molecules having the same sequences as the selected RNAs. Any reaction or combination of reactions known in the art can be used as appropriate, including direct DNA replication, direct RNA amplification and the like, as will be recognized by those skilled in the art. The amplification method should result in the proportions of the amplified mixture being essentially representative of the proportions of different sequences in the mixture prior to amplification. It is known that many modifications to nucleic acids are compatible with enzymatic amplification. Modifications that are not compatible with amplication can be made after each round of amplification, if necessary.

"Randomized" is a term used to describe a segment of a nucleic acid having, in principle, any possible sequence over a given length. Randomized sequences will be of various lengths, as desired, ranging from about eight to more than one hundred nucleotides. The chemical or enzymatic reactions by which random sequence segments are made may not yield mathematically random sequences due to unknown biases or nucleotide preferences that may exist. The term “randomized” is used instead of “random” to reflect the possibility of such deviations from non-ideality. In the techniques presently known, for example sequential chemical synthesis, large deviations are not known to occur. For short segments of 20 nucleotides or less, any minor bias that might exist would have negligible consequences. The longer the sequences of a single synthesis, the greater the effect of any bias.

A bias may be deliberately introduced into a randomized sequence, for example, by altering the molar ratios of precursor nucleoside (or deoxynucleoside) triphosphates in the synthesis reaction or the ratio of phosphoramidites in the chemical synthesis. A deliberate bias may be desired, for example, to affect secondary structure, to introduce bias toward molecules known to have facilitating activity, to introduce certain structural characteristics, or based on preliminary results.

In its most basic form, the SELEX process may be defined by the following series of steps:

1) A candidate mixture of nucleic acids of differing sequence is prepared. The candidate mixture generally includes regions of fixed sequences (i.e., each of the members of the candidate mixture contains the same sequences in the same location) and regions of randomized sequences. The fixed sequence regions are selected either: (a) to assist in the amplification steps described below, (b) to mimic a sequence known to bind to the target, or (c) to enhance the concentration of a given structural arrangement of the nucleic acids in the candidate mixture. The randomized sequences can be totally randomized (i.e., the probability of finding a base at any position being one in four) or only partially randomized (e.g., the probability of finding a base at any location can be selected at any level between 0 and 100 percent).

2) The candidate mixture is contacted with the selected target under conditions favorable for binding between the target and members of the candidate mixture. Under these circumstances, the interaction between the target and the nucleic acids of the candidate mixture can be considered as forming nucleic acid-target pairs between the target and those nucleic acids having the strongest affinity for the target.

3) The nucleic acids with the highest affinity for the target are partitioned from those nucleic acids with lesser affinity to the target. Because only an extremely small number of sequences (and possibly only one molecule of nucleic acid) corresponding to the highest affinity nucleic acids exist in the candidate mixture, it is generally desirable to set the partitioning criteria so that a significant amount of the nucleic acids in the candidate mixture (approximately 5-50%) are retained during partitioning.

4) Those nucleic acids selected during partitioning as having the relatively higher affinity to the target are then amplified to create a new candidate mixture that is enriched in nucleic acids having a relatively higher affinity for the target.

5) By repeating the partitioning and amplifying steps above, the newly formed candidate mixture contains fewer and fewer unique sequences, and the

average degree of affinity of the nucleic acids to the target will generally increase. Taken to its extreme, the SELEX process will yield a candidate mixture containing one or a small number of unique nucleic acids representing those nucleic acids from the original candidate mixture having the highest affinity to the target molecule.

The SELEX Patent Applications describe and elaborate on this process in great detail. Included are targets that can be used in the process; methods for partitioning nucleic acids within a candidate mixture; and methods for amplifying partitioned nucleic acids to generate an enriched candidate mixture. The SELEX Patent Applications also describe ligands obtained to a number of target species, including both protein targets where the protein is and is not a nucleic acid binding protein.

SELEX provides high affinity ligands of a target molecule. This represents a singular achievement that is unprecedented in the field of nucleic acids research. The present invention applies the SELEX procedure to more complicated tissue targets.

Negative selection (Counter-SELEX) is optionally employed before, during or after the Tissue SELEX process. The negative selection provides the ability to discriminate between closely related but different tissue types. For example, negative selection can be introduced to identify nucleic acid ligands that have a high specificity for a tumor cell but do not recognize the cognate normal tissue. Similarly, nucleic acid ligands can be identified which specifically recognize atherosclerotic arterial tissue but not normal arterial tissue. Nucleic acid ligands which recognize fibrin, but not fibrinogen can also be identified by this method. Additionally, nucleic acid ligands to a cell type which express a certain receptor can be counter-selected with a cell line engineered not to express the receptor (or other such macromolecule).

One of ordinary skill in the art will readily understand that various mechanisms can be employed to accomplish this negative selection. The following examples are provided mostly for illustrative purposes and are not meant in any way as limiting the procedures of negative selection. Negative

selection or Counter-SELEX methods were first described in United States Patent Application Serial No. 08/134,028, filed October 7, 1993, entitled "High-Affinity Nucleic Acid Ligands that Discriminate Between Theophylline and Caffeine", which is herein incorporated by reference. A particular implementation of negative selection is embodied using equilibrium partitioning. In this method, two cell lines or other tissue types are separated by a semi-permeable membrane (0.45-0.90 μm pore size) in an equilibrium dialysis chamber; one cell line is the neoplastic target cell line, the other, the normal tissue used for the negative selection. The choice of cell or tissue type for the negative selection will be determined by the specific end results desired and will sometimes consist of a non-malignant cell line of the same tissue type as the neoplastic target. For other experiments, various normal cell types could be combined to create the negative epitope "sink." The random pool of nucleic acids is placed into the dialysis chamber (on the side of the normal cells; this avoids background from high avidity targets which are common to both the tumor and normal cells) and allowed to equilibrate between the two cell lines. Those nucleic acid sequences that remain bound to the target cell line or tissue at equilibrium are selectively recovered and amplified for the next round of SELEX.

This example of negative selection methodology is quite powerful. First, equilibrium dialysis negative selection allows the positive and negative selection to be carried out *simultaneously*. Second, the stringency of the negative selection can be varied through the alteration of the relative amounts of "positive" and "negative" cells placed on each side of the dialysis membrane. These two characteristics of equilibrium dialysis negative selection allow precise control over the evolution of nucleic acid ligands specific for the target cell or tissue type.

This same type of equilibrium partitioning negative selection can be carried out with adherent cell lines. In this embodiment, monolayers of target and negative cells or tissues are plated in different wells of a multi-welled plate. After adherence, media, along with an oligonucleotide pool, is added such that the wells are connected by the volume of cell media. After equilibration of the oligonucleotide pool, those sequences bound by the target cell line or tissue type

would be isolated and amplified for the next round of SELEX.

The equilibrium negative selection strategies above offer a powerful way of generating nucleic acid ligands to tissue targets and especially tumor associated antigens (TAAs).

Additionally, there are several other negative selection methods, which could be classified as "post-SELEX screening procedures." The most simple of these procedures is the testing of individual nucleic acid ligands (those sequences generated by tissue SELEX and demonstrated to be high-affinity ligands for the tissue target) against normal tissue for cross-reactivity. However, this approach is a tedious and time-consuming process.

A more fruitful "post-SELEX" method is to perform a negative selection, for example using a normal tissue as the negative selection target, on a pool that has already been evolved from a SELEX against a desirable complex tissue target, for example a transformed cell line. This example would suggest the performance of two to three negative selections on a normal tissue using a late-round, highly evolved pool from a SELEX of a transformed cell line. The binding of certain sequences to the normal tissue would be used to subtract these sequences from the evolved pool. This method allows one to quickly eliminate from several hundred to several thousand nucleic acid sequences that show a high affinity for those targets common to both the normal and the transformed cell lines.

Another "post-SELEX" screening method is a variation of a photocrosslinking experiment. As an example, it is possible to synthetically incorporate a highly photoreactive nitrine group (which is also iodinatable) on the 5' end of a PCR primer used in the tissue SELEX protocols. Late-round pools from for example, a tumor cell line SELEX would be amplified with this photoactivatable (and ^{125}I-labeled) primer, and this sequence pool would then be irradiated in the presence of the tumor cell line, and in the presence of normal tissue. Membrane proteins would be isolated and solubilized for analysis on an SDS gel. One would expect to see many different protein epitopes tagged by specific oligonucleotide sequences, for both the tumor and the normal cell lines. A few tagged targets will be unique to the tumor cell line. Because the

oligonucleotides have been photochemically linked to the protein targets in a manner which does not destroy the base sequence of the oligonucleotide, it is possible to isolate a tumor-specific band from an SDS gel, and use PCR to recover a specific sequence motif that recognizes a particular tumor antigen. Thus, in one step, it will be possible to remove from a pool oligonucleotide sequences that recognize possibly hundreds of cell surface antigens, leaving one or a few families of sequences that binds specifically to a single tumor-specific antigen.

As described above, the Tissue SELEX methods can include the identification of macromolecules which comprise new epitopes on the tissue target. The nucleic acid ligand to the new epitope component of the macromolecule can be employed to purify, identify and characterize the macromolecule. The new macromolecule can be a previously unknown protein or peptide, lipid, carbohydrate, etc. Virtually any molecule that is part of the molecular make-up of a tissue can be identified by the Tissue SELEX process.

In order to fully exploit this aspect of the invention, it is important to develop strategies for the purification and identification of new macromolecules which comprise the new epitopes and to determine the roles these new macromolecular components of the tissue play in biological systems. The methods for purifying new macromolecules are well-known, especially in the art of protein purification. These standard purification methods include crosslinking, affinity chromatography, peptide microsequencing, Edman sequencing, mass spectrometry, and cDNA library searches.

The following discussion describes this process as it would be applied to the identification of a new tumor-associated antigen (TAA). For the purposes of this discussion, a TAA is a macromolecule that is expressed on a tumor cell, but not on a similar normal cell. A TAA may or may not be immunogenic. A TAA is merely one example of the kind of macromolecules which can be identified by the Tissue SELEX process and simply used for illustrative purposes. However, it is readily apparent that this process can be extrapolated to any new macromolecule identified by the Tissue SELEX process.

As applied to TAAs, the identification of new TAAs by the Tissue SELEX process is composed of two main parts: one, developing strategies for the purification and identification of new TAAs, and two, the elucidation of the role these tumor antigens play in cancer (i.e., determining the biological significance of each particular TAA in the development and progression of a particular cancer).

The steps of purification and identification of most of the TAAs should be straightforward and understood by one skilled in the art of protein purification. As with antibodies, SELEX provides a reagent –a high-affinity ligand specific for the tumor antigen– that is incredibly useful for the purification of the antigen from whole cells or other tissues. As a non-limiting example, most antigens will be amenable to some type of photo-affinity crosslinking or in the negative selection strategies section above. Specific crosslinking of the TAA, using a photoactivatable oligonucleotide with a 3' biotin conjugate will allow one-pass purification of the TAA target using strepavidin coated beads. An alternative method to this purification strategy is to use a column-bound high-affinity nucleic acid ligand to affinity purify the TAA target from solubilized target cell membrane preparations.

There are many compelling reasons to believe that the method provided herein for identifying macromolecules that comprise new epitopes on tissues offers distinct advantages over traditional methods of new macromolecule discovery. Again, the following discussion will be directed to tumor-associated antigen discovery, but one will readily understand that it can be broadly extrapolated to all new macromolecule discovery.

As applied to tumor-associated antigens, one must fully consider that all that is known about tumor antigens has been derived from the immune system's reaction to particular antigens; science has depended on the particular restrictions of the immune system. and the system's repetoires to distinguish antigenic differences between neoplastic and normal tissue. It is entirely possible that other tumor antigens exist that are not subject to immune response. Some investigators have hypothesized that there may in fact be many antigenic differences between cancer and normal tissue. which are. unfortunately, not immunogenic .

The SELEX methodology provides an improved way to identify TAAs that avoids the restrictions posed by the immune system:

a. SELEX can actually provide a deeper search of TAAs than can the entire potential antibody repertoire of an organism– the size of the nucleic acid libraries used in SELEX is unrivaled by any biological system;

b. SELEX provides nucleic acid ligands to targets, including those which are not antigenic to the immune system because of tolerance. Many of the TAAs which have been identified are oncofetal– they are antigens expressed at some point during development or cell differentiation. As prior "self" antigens, they elicit no overt immune response because of earlier immune system tolerization. A SELEX-based search for TAAs avoids the circular nature of using the immune system as a means of identifying tumor antigens;

c. SELEX nucleic acid ligands have been shown to be exquisitely sensitive to target conformation. While most antibodies recognize conformational, or discontinuous eptitopes, antibody functional eptitopes are composed of only a few amino acids. The potential binding surface of an oligonucleotide ligand is much larger than that of an antibody variable region, and may provide greater conformational discrimination of large targets. Additionally, cross-reactivity for SELEX ligands is substantially less of a problem than for monoclonal antibodies. A considerable set of restrictions also controls T-cell mediated tumor responses. These immune system limitations provide important biological functions; however, they limit the immune system's power for TAA identification.

d. SELEX is possibly more sensitive to small quantities of antigen than the immune system. Although the immune system's threshold for reactivity has been estimated to be 200 copies/cell for an antigenic MHC-presented peptide, a B-cell antibody response (necessary for any antigen that is not a peptide– carbohydrates, lipids or conformational antigens) to a monovalent target requires antigen concentrations of about 100 mM. SELEX can generate ligands to TAA targets with a low representation on the cell surface;

e. SELEX provides a rapid and thorough method of TAA discovery. Screening of monoclonal antibodies to tissue sections, and purification and identification of MHC peptides are painstaking processes that set practical limits on the depth and completeness of searches for TAAs. Tissue SELEX experiments take a much abbreviated length of time.

Nucleic acid ligands to tissue targets or the tissue epitopes identified by the method of the invention are useful as diagnostic reagents and as pharmaceuticals. The nucleic acid ligands are also useful for the identification of new macromolecules. The nucleic acid ligands are useful in any application that would be suitable for use of an antibody.

As diagnostic reagents, the ligands or tissue epitopes can be used in both *in vitro* diagnostics and *in vivo* imaging applications. The SELEX method generally, and the specific adaptations of the SELEX method taught and claimed herein specifically, are particularly suited for diagnostic appliations. SELEX identifies nucleic acid ligands that are able to bind targets with hgh affinity and with surprising specificity. These characteristics are, of course, the desired properties one skilled in the art would seek for a diagnostic ligand. Details regarding use of the ligands in diagnostic applications is well known to one of ordinary skill in the art. Nucleic acid ligands that bind specifically to pathological tissues such as tumors may have a role in imaging pathological conditions such as human tumor imaging and even therapeutic delivery of cytotoxic compounds or immune enhancing substances.

The nucleic acid ligands of the present invention may be routinely adapted for diagnostic purpses according to any number of techniques employed by those skilled in the art. Diagnostic agents need only be able to allow the user to identify the presence of a given target at a particular locale or concentration. Simply the ability to form binding pairs with the target may be sufficient to trigger a positive signal for diagnostic purposes. Those skilled in the art would also be able to adapt any nucleic acid ligand by procedures known in the art to incorporate a labelling tag in order to track the presence of a ligand. Such a tag could be used in a number of diagnostic procedures.

Specifically, oligonucleotide ligands with high specificity for particular tumor antigens could become as important as monoclonal antibodies for the detection, imaging, and surveillance of cancer. Modified nucleic acid ligands show nuclease resistance in plasma. and the use of 5' and 3' capping structures will provide stability in animals that rivals that of monoclonal antibodies (and without the immunogenicity of animal-derived MAbs). Radionuclides, magnetic compounds, and the like can be conjugated to tumor-specific oligonucleotides for cancer imaging. SELEX tumor ligands can also be used to determine if these tumor antigens are sloughed off tumors, and are detectable in the plasma like PSA.

The nucleic acid ligands to tissue targets or newly identified macromolecules components of tissue are also useful as pharmaceuticals. Therapeutic uses include the treatment or prevention of diseases or medical conditions in human patients. Therapeutic uses also include veterinary applications. The ligands can bind to receptors and be useful as receptor antagonists. Conversely, under certain circumstances the ligands can bind to receptors and cause receptor capping and act as receptor agonists.

In order to produce nucleic acids desirable for use as a pharmaceutical, it is preferred that the nucleic acid ligand (1) binds to the target in a manner capable of achieving the desired effect on the target; (2) be as small as possible to obtain the desired effect; (3) be as stable as possible; and (4) be a specific ligand to the chosen target. In most situations, it is preferred that the nucleic acid ligand have the highest possible affinity to the target.

Standard formulations can be used for the nucleic acid ligands of the invention and are known to one of ordinary skill in the art.

The following examples provide a non-limiting description of the present invention. Example One describes obtaining ssDNA ligands to the complex tissue target peripheral blood mononuclear cells (PBMC). Ligands to PBMC have many uses including imaging lymph nodes for cancer screening and flow cytometry uses for AIDS monitoring.

Example Two describes the ability to obtain RNA ligands to human fibrin clots. The pyrimidine residues of these RNA ligands have been modified with

flourines at the 2'-position of the sugar. The fibrin ligands are useful as diagnostic agents as described below.

Circulating fibrinogen is cleaved to insoluble fibrin by the actions of the common product of the intrinsic and extrinsic coagulation cascade, thrombin. Fibrin provides a fibrous network for the clot allowing platelet deposition and later fibroblast invasion. Fibrin is present in large amounts in all thrombi, relatively less in platelet-rich arterial clots than fibrin-rich venous clots. Fibrin also can provide the nidus for atherosclerotic plaques and restenotic lesions by harboring thrombin and other mitogens which can lead to endothelial activation and smooth muscle cell proliferation.

The noninvasive detection and localization of thrombi remains a major challenge in clinical diagnosis. Deep vein thrombosis (DVT) and pulmonary embolism (PE) carry with them a high rate of mortality and morbidity. Deep-vein thrombosis (DVT) is a major complication of hospitalization and is diagnosed by physical exam less than one third of the time. Patients at risk include those with a major medical illness, malignancy, undergoing general abdominal, thoracic surgery or major orthopaedic surgery. High risk patients carry a 40-80% risk of DVT with a 1-2% risk of fatal pulmonary embolism (PE) (Weinmann, E.E. and Salzman, E.W. (1994) New Engl. J. Med. 331:1630-1641). PE accounts for 50,000 deaths/yr. 90% of PEs are non-fatal but carry significant morbitiy: dyspnea, pulmonary infarction, abcess, or hypertension. 95% of PEs arise as a complication of DVT. Diagnosis of these conditions is difficult and has not improved, as noted by the high rate of undiagnosed PE on autopsy, which has not improved over time. Freiman et al found evidence of subclinical PE in 64% of consecutive autopsies among persons with various causes of death (Freiman. D.G., Suyemoto, J. and Wessler, S., (1965) N. Engl. J. Med., 272, 1278-1280). Arterial thrombus, mostly secondary to atheromatosis, is even more difficult to diagnose non-invasively.

Non-invasive imaging of venous clots has relied on ultrasonic visualization of the deep venous system of the lower extremities. These studies are limited (generally only the thigh region) and are extremely operator dependent. PE

diagnosis is generally done by ventilation and perfusion scanning using radioisotopes with the gold-standard being invasive pulmonary angiography. Radiolabeled fibrinogen has been used historically (Lensing, A.W. and Hirsch, J. (1993). It requires either prospective administration or thrombus extension after it becomes clinically apparent. A number of reports of radiolabeled antibodies to either fibrin or platelets have been reported. These are sensitive but slow, with adequate images appearing 12-48 hours after injection of the tracer. The need for delayed images is due to clearance of the unbound antibody from the vasculature to allow for adequate signal-to-noise ratio. No significant imaging of coronary artery disease has been reported. The conjecture is that the thickness of the blood pool in the left ventricle of the heart significantly obscures the signal from the small overlying epicardial coronary arteries. Arterial imaging has been performed on the larger vessels of the aorta or femoral arteries using either anti-fibrin or anti-platelet antibodies. Both antibodies have problems: the antifibrin Abs bind to epitopes that are poorly accessible and which are constantly changing through clot stabilization and fibrinolysis; the anti-platelet Abs bind to epitopes which exist in circulating blood, thereby increasing their background. Meaningful high resolution detection of disease in small arteries will require high specificity, rapid clearance of unbound material, and probably 3-dimensional tomographic imaging technologies. In many respects, RNA ligands are suitable agents for these diagnostic approaches. A superior non-invasive diagnostic test for pulmonary embolism would be particularly clinically relevant.

Example Three describes the ability to obtain RNA ligands to rat stenotic carotid arteries. The stenotic carotid arteries ligands are useful as diagnostic and pharmaceutical agents as described below.

Atherosclerosis is one of the major causes of mortality in the world. There has been much effort in identifying and targeting both therapeutics and diagnostic agents to this pathological tissue. Experimentally atherosclerosis suffers from the absence of ideal animal models. Rodent vessels are significantly different from the primate especially with respect to the neointima. Primate model are expensive. The pig or 'minipig' provides a model for restenosis but does not

provide a good model of primary atherosclerosis. Recently, transgenic mouse models have become available, but they are still poorly defined.

Although mechanisms and components of atherosclerosis are not completely defined most investigators would agree that smooth muscle cells play an important role. The consensus is that these SMCs proliferate within the intima and are in some form 'activated'. The rat ballon-injured carotid artery model is one of the best understood models of response to arterial damage. Although there are limits to this model, there is clear evidence that in response to endothelial damage a proliferative response occurs primarily involving the SMCs. Many unique proteins have been identified from this tissue as well as signals responsible for SMC activation, migration and proliferation, as well as, extracellular matrix deposition. As such this remains a viable model of restenosis and less directly, primary atherosclerosis.

The rat balloon-injured carotid (RBIC) model provides a unique model for testing the hypothesis that nucleic acid ligands can be evolved by the SELEX methodology which is capable of recognizing pathological tissue to the exclusion of closely related normal tissue. RBIC are relatively well understood with respect to their composition and structure, are easily and reproducibly produced in a readily available lab animal, and has relevance to human pathologic conditions.

Example One

ssDNA Ligands to Peripheral Blood Mononuclear Cells (PBMC)

This example demonstrates the ability to obtain ssDNA ligands to the complex tissue target human peripheral blood mononuclear cells (PBMC). PBMC are isolated from whole blood as described below and contain a complex mixture of cell types including B-lymphocytes, T-lymphocytes and monocytes. Ligands to PBMC have many uses including imaging lymph nodes for cancer screening and flow cytometry uses for AIDS monitoring.

A. MATERIALS and METHODS

Isolation of PBMCs

Fresh human blood was collected in heparinized vacutainers and up to 35 ml of whole blood was layered atop 10 ml of ficoll (Sigma Histopaque-1077®) in a 50 ml polyethylene conical tube. The samples were centrifuged at 400 x g for 30 minutes at room temperature to separate the blood into three layers: red blood cells (RBCs) below the ficoll, peripheral blood mononuclear cells (PBMCs, including B lymphocytes, T lymphocytes, and monocytes) immediately above the ficoll, and acellular plasma above the PBMCs. Following centrifugation, the plasma was aspirated with a pasteur pipet to within 0.5 cm of the opaque PBMC interface. The PBMC interface, also referred to as the "buffy coat", was transferred to a 15 ml conical tube with a pasteur pipet, 10 ml of phosphate buffered saline solution (PBS, 137 mM NaCl, 2.7 mM KCl, 10.1 mM Na_2HPO_4, 1.8 mM KH_2PO_4) was added, and the cells were washed by gentle aspiration. The cells were then centrifuged at 250 x g for 10 minutes at room temperature and the supernatant aspirated and discarded. The cell pellet was resuspended in 5 ml PBS, mixed by gentle aspiration, centrifuged at 250 x g for 10 minutes at room temperature, and the supernatant aspirated and discarded. This washing step was repeated a third time, and the cells were resuspended in a final volume of 0.3 ml PBS, transferred to a 1.7 ml eppendorf tube, and stored on ice. PBMC yield and viability were measured by diluting the cells 1:50 in PBS, adding an equal volume of 0.4% trypan blue, and counting viable cells with a hemocytometer. Typical yields were 10^6 cells/ml of whole blood with > 95% viability.

Generation of Degenerate ssDNA Library

A library of synthetic DNA oligonucleotides containing 40 random nucleotides flanked by invariant primer annealing sites (oligonucleotide 1, 5'-AGGGAGGAC GATGCGG-$[N]_{40}$-CAGACGACTCGCCCGA-3') (SEQ ID NO: 1) was amplified by the Polymerase Chain Reaction (PCR) for three cycles using oligonucleotides 2 (5'-AGGGAGGACGATGCGG-3') (SEQ ID NO: 2) and 3 (5'-$(Biotin)_3$-TCGGGCGAGTCGTCTG-3') (SEQ ID NO: 3) as primers. Oligonucleotide 3 had three biotin phosphoramidites conjugated to its 5' terminus. The 72 nucleotide double stranded product was denatured by adding an equal volume of formamide and heating to 95°C for 3 minutes, and electrophoresed on

an 8% polyacrylamide gel containing 8 M urea. The DNA strand lacking the biotin tag migrates faster than the biotinylated strand. and was isolated by excision from the gel, elution by squashing in 0.4 ml 2 mM EDTA and gentle agitation for 15 minutes, and centrifugation for 5 minutes using a microcentrifuge filter unit (CoStar Spin-X) to partition the ssDNA from the gel slurry. The recovered ssDNA was precipitated with 0.5 M NaCl and 2 volumes of ethanol, pelletted by centrifugation, washed once with 0.4 ml 70% ethanol, dried, and resuspended in deionized, distilled water (ddH2O).

Selection for PBMC Affinity and Amplification

The affinity of the degenerate ssDNA library for PBMCs was determined using a cell-excess nitrocellulose filter binding assay as described in (Carey, et al. (1983) Biochemistry 22:2601-2609. Since the number of possible DNA binding targets on the surface of a PBMC is unknown, affinity values are reported as the concentration of cells (in units of cells/μl) showing half saturation in this assay. Selections for PBMC affinity were performed under DNA-excess conditions predicted to saturate available target sites, with heparin (Calbiochem, average M.W. 5000) added in excess of DNA to act as a non-amplifiable competitor and to increase stringency. PBMCs, DNA, and heparin were equilibrated for 15 minutes at 37°C and PBMC:DNA complexes were partitioned from free DNA by filtration. PBMC-independent (background) retention of DNA was measured by filtering a similar reaction lacking PBMCs. Filters were prewet with 1 ml of wash buffer (50 mM Tris Acetate, pH 7.4) and following application of the sample, washed with 5 ml of wash buffer to remove unbound DNA. For selections 9-21, 0.5 M urea was added to the wash buffer to further reduce background retention. To minimize the likelihood of enriching for DNA with an affinity for the filter. we alternated among three different filter types: nitrocellulose (Millipore, Type HA. 0.45 μm), acrylic-coated nylon (Gelman Sciences, Versapor-450, 0.45 μm) and glass microfibre (Whatman, GF/C).

For the first selection, 1.4 μM DNA (70 pmoles or about 4 x 10^{13} molecules) was equilibrated with 100 μM heparin and PBMCs at final concentrations of 40.000, 20,000, 10,000, 5.000. and 2.500 cells in 50 μl PBS.

The fraction of total DNA complexed to PBMCs and retained by the filters was calculated by measuring Cerenkov radiation in a scintillation counter. A plot of fraction of DNA bound as a function of total DNA gives a linear relationship with a slope equal to the number of DNA molecules bound per cell (an estimate of the number of DNA binding targets per cell). For each subsequent selection. 5-9 PBMC concentrations were tested and plotted in this fashion and the DNA/cell value recorded. In an additional effort to reduce enrichment for filter binders each selection, the filter with the cell concentration retaining between 1% and 10% of total DNA, and if possible, at least 10 times more DNA than PBMC-independent (background) retention, was chosen for further amplification and enrichment. The selected DNA was harvested from the filter as described in (Tuerk and Gold (1990) Science 249:505-510, amplified by PCR, and size-purified by electrophoresis on an 8% polyacrylamide, 8 M urea gel as described above. As enrichment progressed through successive selections, stringency was increased by decreasing the DNA concentration, increasing the heparin concentration, and for selections # 12 - 21, performing the selections in fresh human plasma instead of PBS. Performing selections in plasma adds an element of specificity, as PBMC-binding DNA molecules with a higher affinity for a plasma component will be depleted from the library. The DNA. PBMC, and heparin concentrations. as well as other relevant selection data, are summarized in Table 1.

Cloning and Sequencing Isolates

Following selection #21, 2 pmol of the selected library was amplified by PCR using oligonucleotide 4 (5'-CCGAAGCTTAATACGACTCACTATAGGGAGGAC GATGCGG-3', containing a Hind III restriction endonuclease cleavage site. underlined) (SEQ ID NO: 4) and oligonucleotide 5 (5'-GCCGGATCCTCGGGCGAGTCGTCTG-3'. containing a Bam HI site. underlined) (SEQ ID NO: 5) as primers. The double-stranded product was size-purified on an 8% polyacrylamide gel and recovered as described above. Fifteen pmol of the PCR product was digested with Hind III and BamHI, along with 1 pmol pUC19 (all from New England Biolabs) for 3 hours at 37°C. Following digestion, the sample was extracted once each

with one volume of phenol and chloroform and recovered by precipitation as described above. The selected library was ligated into pUC19 with DNA ligase (New England Biolabs) for 3 hours at 37°C and the ligation product introduced into *E. coli* DH1α cells by electroporation transformation. Vectors from successful transformations were isolated using a standard plasmid mini-prep protocol and sequenced by dideoxy extension of end-labeled oligonucleotide 6 (5'-TTCACAC AGGAAACAG-3')(SEQ ID NO: 6) with Sequenase T7 DNA Polymerase (United States Biochemical). For a detailed description of these techniques, refer to (Schneider. et al. (1993) FASEB 7:201-207. Larger quantities of individual ligands (>20 pmol) were prepared by amplifying the vector inserts by PCR using oligonucleotides 2 and 3 as primers and denaturing and size-purifying the product as described above.

<u>Competition Assay Measuring Disruption of PBMC:DNA Complexes</u>

In a 20 μl reaction containing 100 μM heparin in PBS, 10 nM end-labeled DNA was was equilibrated with a saturating concentration of PBMCs (10,000 cells/μl) for 10 minutes at 37°C. 5 μl of unlabeled competitor DNA was then added to a final concentration ranging from 1.25 nM to 3.2 μM and allowed to equilibrate for 10 minutes at 37°C. Reactions were filtered and the percent of total labeled DNA retained on the filter was recorded.

B. RESULTS

<u>Affinity for PBMCs was Enriched 40-Fold, and is Heparin Dependent</u>

Following 21 rounds of enrichment by selection and amplification, the affinity of the DNA library for PBMCs was enriched by a factor of 40. In a cell-excess titration in PBS and 100 μM heparin, the degenerate library (DNA-0) showed half saturation at 43,500 cells/μl, while the fully enriched library (DNA-21) showed half saturation at 1,000 cells/μl. The difference in affinity between DNA-0 and DNA-21 is heparin dependent and most sensitive in the range of 10-100 μM. Below 10 μM, binding of the random library approaches that of the selected library, while above 100 μM, binding of the selected library begins to decrease and approach that of the random library. The relationship

between heparin concentration and DNA binding demonstrates the ability of heparin to effectively compete for non-specific binding sites on PBMCs.

Enriched Library Consists of Families with Conserved Elements

From the enriched library, 34 members were isolated and sequenced as shown in Table 2 (SEQ ID NOs: 7-39). Of these 34 sequences, 33 were unique, and 29 contained the sequence TAGGG (or a variation one base removed) in two locations within the 40 nucleotide random cassette. When aligned by the TAGGG pentamers, additional conserved elements emerged and were used to classify the isolates into families as shown in Table 2. The sequences of the 34 isolates from the enriched library are aligned by their conserved TAGGG elements (boldface) and classified into families sharing other conserved elements. Only the sequence of the evolved 40 nucleotide cassette is shown in the alignment. The sequences of the invariant flanking regions are shown in the box and are the same as those from SEQ ID NO:1. Runs of 2 or more G residues are underlined. The 10 isolates chosen for further characterization are indicated with a bullet. Computer algorithms were unable to identify any stable secondary structures for the selected ligands, possibly due to an overall lack of pyrimidine residues (particularly C residues) in the random cassette. However, we conservation of a complex higher-order structure cannot be ruled out, as a large number of GG elements (underlined in Table 2 and consistent with the formation of G-quartet motifs) were selected for in the random region and exist upstream in the invariant flanking region.

Isolates from the Enriched Library Bind PBMCs with High Affinity

To compare the affinity of the selected families for PBMCs, one member of each was chosen for a binding assay (indicated with a bullet in Table 2). The affinities of the chosen ligands in PBS and 100 μM heparin ranged from 400 - 3,000 cells/μl except ligand L9, which lacked the conserved TAGGG elements and showed half saturation at 15,400 cells/μl as shown in Table 3.

The Enriched Library Binds PBMCs but not RBCs

A DNA ligand is most useful if it not only shows high affinity binding to PBMCs, but also shows specific binding to PBMCs. Using the cell-excess

binding assay described above, the affinities of DNA-0 and DNA-21 for human PBMCs, rat PBMCs, and human red blood cells (RBCs) were compared. In PBS and 2.5 mM heparin. rat PBMCs mimic human PBMCs in their interaction with each DNA library. In PBS and 100 μM heparin, DNA-21 binds better than DNA-0 to human RBCs, but even at cell concentrations as high as 10^5/μl (saturation conditions for PBMC binding to DNA-21), RBCs show only 5% binding to DNA-21 and less than 1% binding to DNA-0.

DNA:PBMC Complexes are Disrupted by DNA Competitor

A characteristic of dead cells is an inability to pump out internalized DNA. To demonstrate that the DNA binding seen in the binding assays is a measure of complex formation on the surface of viable cells rather than internalization by dead cells, we pre-bound a saturating concentration of PBMCs with radiolabeled DNA-21 and followed with a chase of excess unlabeled DNA-21 at various concentrations. When the data is plotted as the percent of labelled DNA bound as a function of competitor concentration, a sigmoidal relationship is seen showing one-half saturation at approximately 20 nM competitor and approaching zero as the competitor concentration increases. When this data is plotted as a scatchard, two types of interactions are seen: a high affinity interaction with a K_d value of 8 nM and a stoichiometry of 3 x 10^5 DNA/cell, and a low affinity interaction with a K_d value of 460 nM and a stoichiometry of 3 x 10^6 DNA/cell. Internalization of DNA by dead PBMCs is inconsistent with these results, as all of the pre-bound DNA-21 is competed off at concentrations of unlabeled DNA-21 above 1000 nM.

Example Two

2'F RNA Ligands to Human Fibrin Clots

This example describes the ability to obtain RNA ligands to human fibrin clots. The pyrimidine residues of these RNA ligands have been modified with flourines at the 2'-position of the sugar. The fibrin ligands are useful as diagnostic agents as described previously.

A. METHODS

Clot formation

Human blood was collected in EDTA Vacutainer tubes (Becton-Dickenson), spun at 4°C in a clinical centrifuge. Plasma is removed and stored at -70°C. Clots were generated in glass tubes by the addition of $CaCl_2$ to a final concentration of 20 mM, incubated for 12-16 hr at 37°C.

For the SELEX protocol, the clots were generated in the presence of a glass hanger. Clots were washed 2 hr at 20°C by continuous exchange of 125 ml 0.01M HEPES, 0.125 M NaCl, 2 mM Mg Cl_2, pH 7.5 (Fibrin buffer).

For the *in vitro* assays, clots were generated by recalcification of 50 ml plasma in 96-well mtiter dishes. After 12-16 hr in a humidified chamber at 37°C, the clots were washed by 4 x 200 μl buffer changes at 15 min each.

For the *in vivo* pulmonary embolism assay, clots were generated from recalcified plasma as above. Clots from 2 ml plasma were rimmed and centrifuged for 10 min in a clinical centrifuge. They were washed with 2 ml buffer with centrifugation. Clots were then homogenized for 1 min at low speed with a Tissue-Tearor (Biospec Products). Homogenate was washed 3 x 2 ml buffer followed by passage through 18, 20 , 21, 22, and 23 Ga needles respectively. Homogenate was resuspended in 0.5 volumes buffer relative to initial plasma volume.

Generation of RNA Pool

2'F-pyrimidine, 2'OH- purine RNA was used for this SELEX. The initial DNA template, 40N8, was synthesized on a solid-phase automated DNA synthesizer by standard techniques and had the sequence gggagauaagaauaaacgcucaa-40N-uucgacaggaggcucacaacaggc (SEQ ID NO: 40). All subsequent PCR rounds utilized the primers 5'-taatacgactcactatagggagauaagaauaaacgcucaa (SEQ ID NO: 41) and 5'-gcctgttgtgagcctcctgtcgaa (SEQ ID NO: 42) as the 5' and 3' primers , respectively. PCR, reverse transcription and generation of RNA with T7 RNA polymerase was performed as previously described. Transcription of 2'F RNA was performed in the presence of 1 mM each ATP and GTP (in the presence or absence of α-^{32}P-ATP), and 3mM each 2'F UTP and 2'F CTP transcription proceeded for 5-14 hr at 37°C followed by gel electrophoretic purification in the

presence of formamide and 7 M urea.

SELEX Protocol

The general protocol used for this SELEX is outlined in Table 4. Clots from 0.5 ml plasma were immersed in a 1-4 mM soln of 2'F RNA pool in fibrin buffer for 1 hr at 20°C. Clots were washed by immersion with 4 x 1 ml buffer for 30 min each. The clot was then macerated with a sharp blade and shaken vigorously for 1 hr in 0.6 ml phenol and 0.45 ml 7M urea. 0.4 ml $CHCl_3$ is added to elicit a phase separation, followed by centrifugation at 14,000 RPM. The aqueous phase was extracted with equal volumes 1:1 phenol:$CHCl_3$ then $CHCl_3$, and precipitated with 1.5 ml 1:1 isopropanol: ethanol in the presence of NaOAc and tRNA as a carrier. Generally 0.5-10 pmoles RNA was recovered from a SELEX round.

Stringency and specificity were added to the SELEX after the pool showed signs of increased binding in buffer. Initially, after seven rounds of SELEX, the SELEX binding reaction was done in heparin-anticoagulated plasma. Subsequent washes were done in buffer. At later rounds, washes were also performed in heparinized plasma. No attempt was made to alter the clot size or RNA concentration. A first SELEX performed in this manner yielded a significant amount of fibrinogen cross-reactivity. A second SELEX was performed which diverged from the first at round six, at which time a fibrinogen 'Counter-SELEX' was added. 1-4 nmoles of a 1 mM transcribed pool RNA was premixed with human fibrinogen to a final concentration of 25 μM. After 15 min incubation at 37°C, the solution was filtered two times through three 1 cm diameter, .45 micron, nitrocellulose filters. This resulted in the removal of 80-90% of the protein. The filtered RNA was requantitated and added to clot SELEX reaction.

Sequence Alignment

CLUSTER Algorithm CLUSTER is a program that performs multiple sequence alignment with reoptimization of gap placement within the growing consensus. The algorithm consists of two parts: sequence alignment and clustering. Sequence alignment uses the dynamic programming algorithm of Altschul and Erickson (Altschul and Erickson (1986) Bulletin of Mathematical

Biology 48:603-616) with a weight vector selected on an *a priori* statistical basis, namely, a match = 1.0, mismatch = -1/3, gap opening = -1.0 and gap extension = -1/3. The total cost of alignment is the sum of each pairwise alignment within the consensus. utilizing the quasi-natural gap costs of Altschul (Altschul (1989) J. Theoretical Biology 138: 297-309). Normalization of alignment costs allows for comparison between alignments that contain different numbers of sequences. The normalization used in CLUSTER compares an alignment to the best possible one in which every position matches. A normalized score is the cost of alignment divided by the cost of the best possible alignment. The K-Means algorithm clusters sequences into families. Here, the algorithm is modified slightly from the original version (Tou and Gonzales (1974) *Pattern recognition principles* (Addison-Wesley Publishing Company) to accommodate cost of alignment as the distance measure. Convergence occurs when there is only one family, or the cost to combine any two clusters is beyond a threshold. Optimization (Step 3) pulls out subsets of sequences and realigns them as described by (Subbiah and Harrison (1989) J. Mol. Biol. 209:539-548).

Fibrinogen binding

Fibrinogen binding was determined by standard nitrocellulose filter binding assays as described in the SELEX Patent Appliations.

In vitro clot assay

To 50 µl clot in microtiter wells was added 5,000 or 25,000 CPM (~.5 or 2.5 pmoles) in 100 µl. Clots were incubated for 1 hr followed by 4 x 200 µl buffer washes at 15 min each. Microtiter wells were counted directly in the presence of scintillant.

In vivo pulmonary embolism assay

Clot homogenate prepared as above from 200 µl plasma was admixed with 100 pmoles (~1 x 10^6 CPM) for 15 min at 22°C just prior to injecting suspension via a 23-ga needle into the tail vein of a 200-250 gm Sprague-Dawley male rat. At predetermined times, the animal was sacrificed by exsanguination followed by removal of the lungs. The left lung, which consists of only one lobe, was pressed onto Whatman one paper and then dried on a gel dryer at 80°C for 2 hr and

subjected to autoradiography. The multi-lobar right lung was homogenized in 1 ml buffer and quantitiated in scintillant.

Histologic autoradiography

To visualize clot-bound RNA, histologic autoradiography was employed. RNA was 5'-end-labeled with γ-^{32}P-ATP. Binding was performed as described for the SELEX reactions or for the *in vivo* pulmonary embolism assay. Tissues are fixed at least 24 hours in 10% neutral buffered formalin, processed to paraffin, and made into 5μm sections on poly-L-lysine slides. After drying in 60°C oven, they are deparaffinized and rehydrated prior to exposure. Lungs were perfused with normal saline via the right atrium and inflated with 10% formalin prior to removal, fixation and imbedding. Slides were dipped in melted nuclear emulsion (Amersham LM-1), allowed to dry, and exposured at 4°C. Slides were developed in Dektol developer (Kodak), fixed (Kodak Fixer), and stained in Giemsa (Sigma).

B. RESULTS

Two separate SELEXes were performed on fibrin clot as outlined in Table 4. The two SELEXes differed in the degree and method of counter-SELEX. In the first SELEX (termed FC), eleven total rounds were performed. The binding reaction was performed in buffer for the first seven rounds. The binding was done in human heparinized plasma for rounds eight and nine. The final rounds were done in whole human heparinized blood. In all rounds, the clot was washed with Fibrin buffer. The second SELEX (termed FCN) diverged from the first at round six when there was a first indication of enrichment. A 25 μM fibrinogen counter-SELEX was added to each round begining at round six. In addition, the binding reactions were done in heparinized human plasma and the clots were washed with plasma instead of physiologic buffer for rounds 7-14. The final round pools bound 2.5% and 6.4%, respectively, in the presence of heparinized plasma. The round twelve and fourteen pools for the first and second SELEXes, respectively, were sequenced. In both cases RNA sequencing indicated considerable nonrandomness. The pools were amplified with new primers containing EcoR1 and Hind III sites on the 5' and 3' end, respectively, and cloned

into pUC 18.

Visualization of clot binding

The round eleven pool from the initial SELEX was 5'-end labeled with ^{32}P. The pool was admixed with clot in an identical manner to a SELEX in Fibrin buffer. After washing the clot was fixed in formalin, imbedded, sectioned and overlayed with autoradiography emulsion. Development of the sections showed the RNA (visualized as black grains) were coating the outside of the clot with some diffusion into the intertices of the clot. In another experiment, the rat PE model was performed with ^{32}P kinased ligand. The pool was pre-bound to the homogenized clot and injected into the tail vein of a rat. At fifeteen minutes the rat pulmonary bed was perfused with saline via the right atrium. The lungs were inflated and fixed by injection of 10% formalin into the trachea prior to removal and placement in formalin. Tissues were processed as above. Tissues showed black grains only in close association with intravascular clots. There was no evidence of RNA pooling downstream of occluded vessels. Furthermore, when the study was run with a non-evolved round 0 pool no black grains were visualized within the lung.

Sequence analysis and activity screening

Seventy-two clones of each were sequenced (SEQ ID NOS: 43 - 130) . Eighty-eight unique clones were seen and 15 clones differed by only one nucleotide. The sequences were combined for analysis and grouped into sequence motifs by the application of CLUSTER and visual inspection as shown in Table 5. Only the sequence of the evolved 40 nucleotide cassette is shown in the alignment. The sequences of the invariant flanking regions are included in each clone and are the same of those in SEQ ID NO:40. When the unique clones from both SELEXes were combined for CLUSTER analysis they formed 17 separate motifs. 27/88 clones (31 %) were grouped into two major motifs. Motif I and II had 15 and 12 members, respectively. A third motif (Motif III) contained 9 members primarily from the first SELEX and had properties similar to Motif I. Four of the motifs had only two members each.

78/88 (89 %) clones were screened for binding in the qualitative *in vitro* microtiter plate assay. These clones were grouped into high, medium and low affinity with 37, 10, and 31 members in each group, respectively. 46/78 clones screened were further screened for fibrinogen-binding activity. The screen was a standard nitrocellulose binding assay employing a four-point curve from 0.1-10 μM fibrinogen concentration. Sixteen of the clones were further screened for clot binding in the *in vivo* rat pulmonary embolism assay. Results for each of these assays are shown in Table 5.

Of the 27 clones in the major two sequence motifs, 24 were evaluated by the initial screen for binding in the microtiter plate assay. Of those, 15/24 (63 %) were characterized as high-affinity or moderate-affinity clot binders. The fibrinogen-binding screen was also divided into high, moderate and low affinity groups with 14, 6, and 26 in each group, respectively. In the fibrinogen-binding screen, high-affinity binders were included if the Kd<1 mM, while low-affinity binders included those clones with a Kd>1 mM. In Motif I, 10/11 (91%) were in the high- or moderate-affinity for fibrinogen binding while, in Motif II, 0/9 (0 %) fell in the high- or moderate affinity fibrinogen binding groups. Eleven members of Motifs I, II were tested in the *in vivo* PE assay. The clones from Motif I had on average 40% increase in clot binding over Motif II when the binding reaction was performed in buffer. However, when the binding reaction was performed in heparinized plasma, Motif I had a binding decrease by 90 % while Motif II had a decrease of only 10 %. There was a clear distinction between Motif I and II in the degree of fibrinogen binding. Motif I bound clots with a slightly greater degree than Motif II but had a significant degree of crossreactivity. More definitive fibrinogen binding curves indicated that Motif I clones had Kd of 200-600 nM. The Kd(fibrinogen) of Motif II is too high to be quantitated accurately. 1-3% binding was seen at the highest fibrinogen concentration of 10 μM. One can extrapolate a Kd of greater than 100 μM.

Binding Quantitation

The two best binders in the PE model which had the lowest affinity for fibrinogen were pursued. Both of these clones resided in Motif II. Clone 69 (SEQ

ID NO: 55) was analyzed for binding *in vitro* homogenized clot. By adding a fixed amount of radiolabel clone 69 (2 nM) to a fixed amount of clot (200 μliters plasma equivalent) with increasing amount of nonradiolabeled ligand, binding could be quantitated. Analyzing data in a Scatchard format yield a two-component curve with high and low affinity binding components. There were 200 nM high affinity sites per 200 μliters plasma equivalent. The ligand bound these sites with a Kd of 10-20 nM. These sites were saturable. Furthermore, if the ligand was pre-bound to the clot homogenate, it could be competed off the clot by the addition of 3 μM unlabeled clone FC 69 with a half-life of 37 min. The label ligand did not diffuse off the clot homogenate to any significant degree over 4 hours in the presence of buffer alone or 3 mM of a 2' F clone which had no measurable affinity for clots. As such it appears that the binding of a specific ligand to clots is specific and stable.

Clone Truncation

Boundary experiments were performed in which the ligand was radiolabeled on either the 5' or 3' end. The ligand was subjected to partial cleavage by modest alkaline hydrolysis and bound to fibrin. Binding RNAs were purified and sequenced. The results are shown in Table 6. Typically a ladder was seen until a region critical to binding was lost, at which point there is a step-off on the sequencing gel. Duplicating the reaction with both ends labeled allowed the determination of both the 5' and 3' boundary. Boundary studies were performed on one clone from Motif I and two clones from Motif II. All clones could be folded into a putative secondary structure which was consistent with the boundaries. The Motif I could be folded into a 'dumbell' structure. Motif II used a significant amount of the 3'-fixed region. It could be folded into a stem-loop/bulge structure. Based on the boundaries and the structure potentials four nested synthetic 2'F oligonucleotides of clone FC 69 (SEQ ID NO: 55) were synthesized by automated solid-phase synthesizer ranging from 25-41 nucleotides in length (SEQ ID NOS: 131-134). These were tested for binding to homogenized clot by competition with full-length material both *in vitro* and in the rat PE model. In the *in vitro* assay, qualitatively binding was seen with all four clones, 69.4

(SEQ ID NO: 134) (the longest) being the best. In the rat PE model, again, all four truncates bound clot. The two truncates with four additional nucleotides past the boundary on the 3'-end showed 3-fold increased binding over those whose sequence ended exactly at the 3'-boundary. The binding to clots in the lung as normalized to full-length material was 32, 118, 36,and 108% for each of the four truncates, respectively. Furthermore, the binding of the best truncate in this assay, 69.2 (SEQ ID NO: 133)(29-nucleotides), was partially inhibited by the addition of 1 μM unlabeled full-length clone FC 69.

Example Three
RNA Ligands to Stenotic Carotid Arteries

This example describes the ability to obtain RNA ligands to rat stenotic carotid arteries. The stenotic carotid arteries ligands are useful as diagnostic and pharmaceutical agents as described previously.

A. METHODS

Generation of RNA Pool

2'F-pyrimidine, 2'OH- purine RNA was used for this SELEX. The initial DNA template, 40N8, was synthesized on a solid-phase automated DNA synthesizer by standard techniques and had the sequence gggagauaagaauaaacgcucaa-40N-uucgacaggaggcucacaacaggc (SEQ ID NO: 40). All subsequent PCR rounds utilized the primers: 5'-taatacgactcactatagggagauaagaauaaacgcucaa (SEQ ID NO: 41) and 5'-gcctgttgtgagcctcctgtcgaa (SEQ ID NO: 42) as the 5' and 3' primers, respectively. PCR, reverse transcription and generation of RNA with T7 RNA polymerase was performed as previously described. Transcription of 2'F RNA was performed in the presence of 1 mM each ATP and GTP (in the presence or absence of α-^{32}P-ATP), and 3mM each 2'F UTP and 2'F CTP transcription proceeded for 5-14 hr at 37°C followed by gel electrophoretic purification in the presence of formamide and 7 M urea.

SELEX Protocol

250 gm male Sprague-Dawley were subjected to either unilateral or bilateral balloon-injury of the carotids. Rats were anesthetized with isoflourane.

The carotids exposed by a 1 cm midline incision. The common, internal, and external carotid were identified. A #2 French Fogarty catheter was inserted into the external carotid just above the bifurcation and advanced to the aortic arch. The balloon was inflated and pulled back to the bifurcation. This was repeated six times. The catheter was removed, and the external carotid was ligated. The skin was closed by cyanoacrylate glue. Injuries were allowed to develop for 10-14 days.

At the time of SELEX, animals were sacrificed under anesthesia by exsanguination. Both carotid arteries were disected from the bifurction to the aortic arch. The arteries were gently stripped of any associated connective tissue. Twelve rounds of SELEX were performed ex vivo as indicated in Table 7. The first three rounds were done by simply immersing two arteries in a 0.5 ml of a 2μM RNA solution. The binding reaction was rotated at 20°C. Carotid segments were then washed with four 1 ml buffer washes for 15 min each prior to harvesting the bound RNA. Subsequently, two carotid arteries were ligated together in series with a small length of polyethylene tubing. The distal ends were also canulated with tubing for attachment to a syringe pump and collection of eluant. These procedures were done with minimal disruption to the arterial segments. For the SELEX, 0.75-2.3 nmoles in one ml physiologic buffer was passed through the arterial segments at 4 ml/hr. This was followed by washing the segments with an additional 1 ml of buffer at 4 ml/hr. The segments were taken out of line, counted by Cherenkov radiation, and processed for RNA extraction. Rounds 4-7 were performed in this manner with both artery segments having been balloon-injured. All tissue was processed for RNA extraction. In rounds 8-12, an unijured artery was ligated upstream from an injured artery as shown in Figure 1. Perfusion proceeded as above. Both artery segments were counted, but only the injured segment was processed for RNA extraction. Rounds 8-12 were done to 'counter-SELEX' against the evolved RNA binding normal arterial endothelium. In a subsequent control, it was shown that the uninjured artery had an intact monolayer of intimal endothelium by Factor VIII immunohistochemistry.

<u>Tissue Extraction of 2'F-RNA</u>

Carotid segments were minced with a scalpel and homogenized with 1 ml TRIZOL Reagent (Gibco). Homogenate was clarified by centrifugation. phase-separated with $CHCl_3$, and the aqueous phase precipitated with IpOH, all according the manufacturers protocol. Purified RNA was resuspended in H_2O, and digested for 15 min at 37°C with 0.1 U/µL DNAse I (Pharmacia) and 100 µg/ml RNAse A (Sigma) in reverse transcription buffer. 2'F-pyrimidine, 2'OH-purine RNA is stable to RNAse A digestion. The digest was phenol, phenol/CHCl3 extracted and EtOH precipitated out of Na Acetate. The RNA was then subjected to RT/PCR under standard conditions to generate a template for T7 RNA polymerase. After twelve rounds the pool was cloned and sequenced. The sequences identified as C# in Table 8 were obtained by this protocol.

<u>*In Vivo* SELEX</u>

In a subsequent SELEX, 3-5 nmoles of the Round twelve pool was injected directly into the tail vein of a rat with a 14 day unilateral lesion. After 15 min, the animal was sacrificed and the carotids processed. RNA was amplified as before. Four Rounds of n vivo SELEX were done as indicated in Table 7. This pool was cloned and sequenced and the sequences from both cloning steps were combined for sequence analysis. The sequences identified as Civ# in Table 8 were obtained by this protocol.

<u>Binding Analysis</u>

Binding of RNA either as a pool or individual clones was performed by comparing ^{32}P counts bound to normal versus injured carotid artery segments. Binding was visualized by histologic autoradiography in either the ex vivo perfusion system or by overlaying RNA onto fresh-frozen carotid artery slices.

<u>Histologic autoradiography</u>

To visualize carotid-bound RNA, histologic autoradiography was employed. RNA was 5'-end-labeled with γ-^{33}P-ATP. Binding was performed as described for the SELEX reactions. Tissues are fixed at least 24 hours in 10% neutral buffered formalin, processed to paraffin, and made into 5 mm sections on poly-L-lysine slides. After drying in 60°C oven, they are deparaffinized and rehydrated prior to exposure. Slides are dipped in melted nuclear emulsion

(Amersham LM-1), allowed to dry, and exposured at 4°C. Slides are developed in Dektol developer (Kodak), fixed (Kodak Fixer), and stained in Giemsa (Sigma).

Fresh-frozen carotid sections were prepared by imbedding normal or injured carotid artery segments in OCT and freezing at -20°C. 5 μm sections were cut on a cryostat, placed on a slide (typically a normal and injured section were juxtaposed on a single slide), and stored frozen at -5°C. Slides are warmed to room temperature, the paired sections are encircled with a grease pencil, and pre-bound with 30 ml PBS, 0.5% Tween-20, 1 mM low molecular weight heparin (Calbiochem). After 15 min the solution is removed and 30 μl of the same solution containing 10,000 CPM (~1 pmole) 33P-labeled RNA is added for 30 min. Slides are washed twice with PBS/Tween-20, twice with PBS. Slides are fixed in 10% neutral buffered formalin, then rinsed in distilled water prior to exposure.

Sequence Alignment

CLUSTER Algorithm. CLUSTER is a program that performs multiple sequence alignment with reoptimization of gap placement within the growing consensus. The algorithm consists of two parts: sequence alignment and clustering. Sequence alignment uses the dynamic programming algorithm of Altschul and Erickson (Altschul and Erickson (1986) Bulletin of Mathematical Biology 48:603-616) with a weight vector selected on an *a priori* statistical basis, namely, a match = 1.0, mismatch = -1/3, gap opening = -1.0 and gap extension = -1/3. The total cost of alignment is the sum of each pairwise alignment within the consensus, utilizing the quasi-natural gap costs of Altschul (Altschul (1989) J. Theoretical Biology 138:297-309. Normalization of alignment costs allows for comparison between alignments that contain different numbers of sequences. The normalization used in CLUSTER compares an alignment to the best possible one in which every position matches. A normalized score is the cost of alignment divided by the cost of the best possible alignment. The K-Means algorithm clusters sequences into families. Here, the algorithm is modified slightly from the original version (Tou and Gonzáles (1974) *Pattern recognition principles* (Addison-Wesley Publishing Company) to accommodate cost of alignment as the distance measure. Convergence

occurs when there is only one family, or the cost to combine any two clusters is beyond a threshold. Optimization (Step 3) pulls out subsets of sequences and realigns them as described by (Subbiah and Harrison (1989) J. Mol. Biol. 209:539-548).

B. RESULTS

SELEX

Twelve rounds of *ex vivo* RBIC SELEX was performed followed by four rounds of *in vivo* SELEX as indicated in Table 7. Pools were cloned and sequenced after the ex vivo SELEX and the ex vivo/*in vivo* SELEX; the sequences are provided in Table 8. Only the sequence of the evolved 40 nucleotide cassette is shown in the alignment of Table 8. The sequences of the invariant flanking regions are included in each clone and are the same as those of SEQ ID NO:40. The last five rounds of the ex vivo SELEX were done with a normal carotid artery as a negative selection (Counter-SELEX). Evaluation of these rounds indicated that over the last five rounds the injured carotid bound between 0.07-0.5% without a trend towards increased binding in the later rounds. The discrimination between normal and injured was 3.2-4.5, again without a trend toward increased discrimination. At round twelve, the RNA pool was sequenced and shown to be significantly non-random.

The pool was then taken forward in the *in vivo* SELEX. Very little RNA was recovered from the injured carotid arteries (0.2-0.6 pmoles). Comparing CPM in the normal versus injured yielded discrimination values of 2.61-3.54. At the first round of *in vivo* SELEX, equal amounts of round XII RNA and Round 0 RNA were injected into two different animals both with unilateral balloon injuries. There was no discrimination for the Round 0 RNA (i.e. the same number of counts bound the normal as the injured artery), whereas in the round 12 pool. 2.61 times more RNA bound the injured carotid as compared to the uninjured. At Round 15, the evolved pool was injected into the animal or perfused through an ex vivo apparatus exactly as had been done for rounds 8-12. The discrimination of the Round 15 RNA was 4.61, which was higher than had ever been seen during the ex vivo SELEX.

Seventy-two clones from the ex vivo SELEX were sequenced. of which 50 were unique as shown in Table 8. The striking finding was that of the seventy-two clones, two were present in multiple copies. One clone (clone C33 (SEQ ID NO: 146)) had nine identical or one base difference copies, while another (clone C37 (SEQ ID NO: 186)) had ten copies. Thus nineteen of twenty-two copies in the inital sequencing arose from two sequences. Sequences stemming from those two persisted after the *in vivo* SELEX with clones related to C33 generating the largest single family in the combined analysis (Motif I).

Analysis of Clone Binding

Of the ninety-four unique clones from the two SELEX methods, twenty-eight were screened for binding to fresh-frozen rat carotid artery sections. These were qualitatively graded by intesity of staining (+, ++, +++) and specificity (s, ns) as shown in Table 8. Clones were seen with a variety of patterns from no visible binding to strong binding of all tissue components. Specificity was graded based on relative intensity of binding to neointimal tissue over normal or injured media or adventia. Early on C33 (SEQ ID NO: 146) was found to have both increased intensity and specificity over both unevolved Round 0 or Round 12 pool RNA. Further screening uncovered three other clones with better binding characteristics: C59 (SEQ ID NO: 150) , Civ45 (SEQ ID NO: 202) , and Civ37 (SEQ ID NO: 210). Civ41 (SEQ ID NO: 158) was of interest because it was of the same Motif as C33 and C59, but had very intense staining and little specifity: staining neointima, as well as normal an injured media. Civ45 in three independant binding experiments had the most intense staining in a specifically neointimal distribution. This clone also showed an slight increase in binding to injured media over normal media. If smooth muscle cells migrate from the media to the neointima in the injured artery, then it may not be suprising that whatever this clone is binding exists within the injured media. Of the four clones noted with high specificity, two of them are from Motif I and are closely related. Three of the four contain the sequence GUUUG (underlined in Table 8). Putative secondary structures are shown in Table 9. It is unknown at this time whether

these structure correlate to the true structure. In the absence of boundary experiments they provide a basis for truncation studies.

Clone C33 and C59 were ^{33}P-labeled and perfused in an ex vivo manner. Although not quantitated, they showed dramatic binding to the lumenal wall of the damage artery but not to the normal vessel.

C59 was used to stain fresh-frozen section of RBIC of different ages. Carotids were harvested at 1, 2, 4, 6, 8, 16 wks after balloon injury. The neointimal signal was greatest at 2-6 wks. It was minimally present at one wk and dissappear after six. The pattern of staining neointima in the highly specific clones is diffusely granular. Silver grains are not obviously associated with smooth muscle cell bodies. One hypothesis is that the the RNAs are binding to components of the extracellular matrix (ECM). It is known that SMCs require an ECM scaffold to migrate. They have been shown to lay down unique proteoglycans in the course neointimal proliferation. The presence and disappearence of these unique proteoglycans corresponds temporally to the binding of RNAs to neointima. As such one viable possibility is that the RNAs are binding specifically to these proteoglycans.

Table 1
Summary of Selection Parameters and Data for PBMC SELEX

Selection	[DNA] nM	[PBMC] cells/μl	[heparin] μM	Filter Type	% PBMC retention	% bkgd retention	DNA/cell
1	1,400	40,000	100	NC	3.1	0.1	6.0×10^5
2	900	120,000	100	NC	4.7	0.3	2.0×10^5
3	800	92,000	100	GF	3.5	0.8	9.0×10^4
4	480	60,800	100	AN	1.8	0.08	8.7×10^4
5	500	52,500	500	NC	4.6	0.3	2.2×10^5
6	990	18,300	500	NC	1.3	0.05	5.0×10^5
7	750	14,400	2,500	NC	1.6	0.09	2.2×10^5
8	560	47,800	2,500	AN	4.0	0.2	2.8×10^5
9*	100	11,200	2,500	NC	7.2	0.5	9.3×10^4
10*	100	12,600	2,500	AN	3.1	0.6	1.0×10^5
11*	100	5,100	2,500	NC	5.7	0.7	7.3×10^4
12*	50	37,500	2,500 + plasma	NC	2.2	0.1	2.3×10^4
13*	50	75,000	2,500 + plasma	AN	4.9	0.3	2.2×10^4
14*	10	32,000	2,500 + plasma	NC	0.9	0.2	1.6×10^3
15*	10	32,000	plasma	NC	3.1	0.3	2.3×10^3
16*	10	112,000	plasma	AN	5.6	0.5	3.1×10^3
17*	10	65,000	plasma	NC	3.0	0.6	3.1×10^3
18*	10	87,300	plasma	AN	4.8	0.5	4.2×10^3
19*	10	118,560	plasma	AN	6.0	0.5	3.3×10^3
20*	10	94,560	plasma	NC	4.0	0.3	3.1×10^3
21*	10	48,000	plasma	AN	7.3	0.7	5.8×10^3

TABLE 2
PBMC SEQUENCES

Degenerate ssDNA Library

5'- AGGGAGGACGATGCGG - $[N]_{40}$ - CAGACGACTCGCCCGA - 3' (SEQ ID NO: 1)
5'fixed region — random region — 3'fixed region

Ligand	Random Region (fixed regions are provided as described above)	SEQ ID NO:
• L49	GGGGTCGGTTCGGGCATA TAGGG TATTCTTCGTA GAGGG	7
L8	GGGGTCGGTTCGGGCATA TAGGG TATTCTTCGTA AAGGG	8
L35	GGGGTCGGTTCGGGCATA TAGGG TATCCTTCGTA GAGGG	9
• L1,L34	CACGT TAGTAGGAT TAGGA TTATTCAGGTTG TAGGG AACA	10
L29	CACGTTCAGCAGGAT TAGGG TTGTTTNGGTTG TAGGG ACACA	11
L18	CACGG TAGTAAGTAG TAGGG TATTATA AT TAGGG GATCCA	12
L21	CACGG CAGTATTATT CAGGG GTCTTAGATAT TAGGG GGCA	13
• L42	CACGGTAGGTTTTAGA TAGGG ATATTTGGTG TAGGG AGCA	14
L5	CACGGTAGGTTATAGA TAGGG ATATTTNTTG TAGGG AACA	15
L11	CACGGTAGGTTTTAGA TAGGG ATATTTGATG TAGGG AGCA	16
L25	CACGGTAGGTTTTAGA TAGGG ATATPTGGTA TAGGG AGCA	17
L36	CACGGTAGGCTTTAGA TAGGG ATATTTGATG TAGGG AGCA	18
• L26	GGGGAG TAGGG TATTTAAAAATGT TAGGG TAAGTTTCCTC	19
L10	GGGGAG TAGGG TATTTAAAAGTGT CAGGG TAAGTTTCCTC	20
• L7	CGTAGTAAGAAGTATTAT TAGGG ATATTG TAGGG GCGCTA	21
L22	CGTAGTAAGAAGTATTAT TAGGG ATATTG CAGGG GCGCTA	22
• L43	GGCAGCAAGA GTTTGAT TAGGG TATAGT TAGGG GCGCTG	23
L19	GCAGCAAGA GTTTGAT TAGGG TATAGT TAGGG GCGCTGC	24
L41	GCAGTAAGG GTTTGAT TAGGG TATAGT TAGGG GCGCTGC	25
L46	GCAGCAAGAGG TTGAT TAGGG TATAGT TAGGG GCGCTG	26
L20	CGGCAAGATGATTGAA TAGGG GATCTAAAGT TAGGG GCGC	27
L6	GCAGCAGG TG TAGGG GTATAGATGGA TAGGG ATTTCTTCT	28
• L28	CACA TAGGG GAAATGA GAATAG TAGGG TATTAATACAGTG	29
L38	CACA TAGGG GAAATGA GAAGAA TAGGG TATTAATACAGTG	30

L50	CAGGT	TAGGG	GAAAGGTTTAATAAT	TAGGG	TATAAAT	GTG	31
L14	CAGGTAGAGA	TAGGG	AAGTTTTATG	TAGGG	GACAATTCGT		32
L44	CAGGTAGAGA	TAGGG	AAGTTTTATG	TAGGG	GACAATTCGT		33
L31	CACAA	TAGGG	AAATTT GTTGTTATAGT	TAGGG	ATACTGGA		34
L40	GGCCGAA	TAGGG	AAATTTA TTATTACT		AACAGTAATCCCC		35
L48	CAGGACT	TAGGG	ATTTAGTTGTTT	TAGGG	GTTATGTAGT		36

L9	GGGGGGATGAGATGTAATCCACATGTCACTTATTAAGTCC	37
L12	CAGGGGATGGGATGTAATCCTCATGTCACTTATTAAGTCC	38
L13	TACGACTACGATTGAGTATCCGGCTATAATATTACCATTG	39

Table 3
Sequences and Affinities of Selected PBMC Ligands

LIGAND	SEQUENCE OF RANDOM REGION	AFFINITY (PBMC/μl)	SEQ ID NO:
DNA-0	Degenerate DNA Library	43,500	1
DNA-21	Enriched DNA Library	1,000	
L1	CACGTTAGTAGGATTAGGATTATTCAGGTTGTAGGGAACA	3,000	10
L7	CGTAGTAAGAAGTATTATTAGGGATATTGTAGGGGCGCTA	700	21
L14	CAGGTAGAGATAGGGAAGTTTTATGTAGGGGACAATTCGT	1,200	32
L26	GGGGAGTAGGGTATTTAAAAATGTTAGGGTAAGTTTCCTC	800	19
L28	CACATAGGGGAAATGAGAATAGTAGGGTATTAATACAGTG	2,400	29
L31	CACAATAGGGAAATTTGTTGTTATAGTTAGGGATACTGGA	1,800	34
L42	CACGGTAGGTTTTAGATAGGGATATTTGGTGTAGGGAGCA	1,100	14
L43	GGCAGCAAGAGTTTGATTAGGGTATAGTTAGGGGCGCTG	700	23
L49	GGGGTCGGTTCGGGCATATAGGGTATTCTTCGTAGAGGG	400	7
L9	GGGGGGATGAGATGTAATCCACATGTCACTTATTAAGTCC	15,400	37

TABLE 4

Serum Clot SELEX 2'F-40N8-RNA

Round	Method	[Clot]	[RNA]	[NaCl]	Wash	Volume, ml	% bound	Yield, pm	Background
FC									
1	clot incubation	500 ul plasma	4.00E-06	125 mM	Buffer	0.5	1	26	
2	"	"	4.00E-06	125 mM	"	"	0.66	12.3	
3	"	"	1.90E-06	125 mM	"	"	0.18	1.6	
4	"	"	4.00E-06	125 mM	"	"	0.18	3.5	
5	"	"	4.00E-06	125 mM	"	"	0.37	7.8	
6	"	"	4.00E-06	125 mM	"	"	2.9	50	
7	"	"	4.00E-06	125 mM	"	"	6.2	81	
8	"	"	3.00E-06	Hep. Plasma	"	"	9	67	
9	"	"	4.00E-06	Hep. Plasma	"	"	4	53	long wash
10	"	"	2.90E-06	Hep. Blood	"	"	7.9	70	
11	"	"	4.00E-06	Hep. Blood	"	"	2.5	46	
FCN									Counter-SELEX
7	clot incubation	500 ul plasma	5.40E-06	Hep. Plasma	Hep. Plasma	0.5	0.7	20	0.025 mM fibrinogen
8	"	"	1.93E-06	"	"	"	1.3	8.6	"
9	"	"	2.47E-06	"	"	"	1.4	15	"
10	"	"	6.00E-07	"	"	"	2.3	4.7	"
11	"	"	2.00E-06	"	"	"	2.6	20	"
12	"	"	3.80E-07	"	"	"	1.8	14	"
13	"	"	1.80E-06	"	"	"	1.9	12	"
14	"	"	2.10E-06	"	"	"	5.1	41	"

TABLE 5

Fibrin-Binding Clones

FINAL CLUSTERS	Sequence	SEQ ID NO	In Vitro Clot Binding	Fibrinogen Affinity	Binding PE Assay
FC1	: AGGGCUCGUGUGCCAAAUCGCUAACAAC-AAGCUAGCUGAU	43	o		
FCN54	: CUGGGCUCAUCCGGCGAAU-GAUG-CAAGGAAGAUUUCACAU	44	o	%	
score 0.365079					
FC3	: AAGGA-UAG-UGUGCU--CCUGUA--CCAAAUUUCCAAAGCGAUAU	45	o		
FC73	: AAAGAGUAA---AGCG--CG-GAA--CAGGAUUCACGUUGCGCUCUU	46	o		
FC75	: AAAGAGUAA---AGCG--CG-GAA--CAGGAUUCACGUUGCGCUCA	47	o		
FCN6	: CAACGAUUAUCUUUUCGGCCGUGAAACCCAAACUGACGCC	48	o	%	
score 0.292824					
FC4	: CGCGAGGAUAGGGUG--CAGCUUCUGUUCCAAAUACGUGA-AU	49	*		
FC12	: UAAGUCGAAGAGCUCCUGAUCCAAACCAUCGA-AAG-GACGU	50	o		
FC28	: GG-UAAGUUG--GAGCUCCUUAUCCAAGCACGCAAUAAGUGAC	51	o		
MOTIF II score 0.355556					
FC6	: UUUGGCGU-GG-GAU-CCUGGA-CUGAAGG--AUUUUGACGAUGC	52	o		
FC45	: AUUCAAGACA-GA-GAC-UUUCCU-U-GAA--U-GCUCUGUCCCAUAA	53			
FC54	: ACAAAUGU-GC-GAC-CUUGGA-C-GAAGUUAACUCGGACGGUUC	54	o		
FC69	: ACAAAUGU-GC-GCC-CUUGGA-C-GAAGUUAACUCGGACGGUUC	55	*	%	$
FC72	: ACAAAUGU-GC-GCC-CUUGGA-C-GAAGUUAACUCGGACGGUUG	56	*	%	
FCN16	: ACAAAUGU-GC-GCC-CUUGGA-C-GAAGUUAACUCGGACGGUUC	57	o	%	
FCN19	: AAGUCU-GA-GACUCCUGGA-CUGAA-UUAGCUAGGACGGCUG	58	*	%	$
FCN30	: UAGGAGCCUAGCAGCC-CCUGCAUC-GA---UCACUAGGAUGGUU	59	*	%	$
FCN38	: AAAGUGUAGC-CUU-CCUGGA-CUGUAGGU-ACUAGGACGGUCC	60	*	%	@
FCN44	: ACAAAUGU-GC-UCC-CUUGGA-C-GAAGUUAACUCGG-CGG	61	*	%	$
FCN55	: AAGAAGCUG-GC-GAC-AGGCGA---AAAGCAGACU-UGAGGGAA	62	o	%	@
FCN72	: AGUAG-GU-GA-GGCUUCUGGA-CUGAAG-UAACUAGGUCGGUUC	63	*	%	@
score 0.339752					
FC8	: CAUGA-GCUGCUGGACCAAA-CAGAUG-GAGG---AACCA-CCGUGU	64	*		
FC39	: GA-GCU-CUUGACGAAAACCUAUGCGAGAUGGAUACU-CGGUU	65			
FC40	: GA-GCU-CUUGACGAAAACCUAUGCGAGAAGGAUACU-CGGUU	66			
FC41	: GA-GCU-CUAGACGAAAACCUAUGCGAGAUG-AUACU-CGGUC	67	o		
FC55	: UGA-GCU-CUUGAAGAAGUCC-----GAAC---AUUCUCCUUUCUGCGACU	68	o		
FC64	: GA-GCUCCGGGAUCCAAGCG--UGCAACA---ACACU-AUGCCCAC	69	o		
FC65	: AAUAC-CCU-CGGGAACCAAUCC-----GACCCU-AUUUUGCAGUUUG	70	*		
FCN59	: AUGAUGCU-CCUGAAGUAAUCACCAG-GAC----AUCCU-CGGCAU	71	o	%	
FC9	: GCAAU--CU-CGGACUAGACCAACGACCUUCGUUUGACGCUC-A	72	o	%	@
FC18	: CCGAUUU--CU-AGGACG-GAUUUACG---GAGAAUUGAGUCGC-AAG	73	o		

Table 5 (cont'd)

FINAL CLUSTERS		Sequence	SEQ ID NO:	In Vitro Clot Binding	Fibrinogen Affinity	Binding PE Assay
MOTIF I		score 0.262803				
FC38	:	A-CGG-CGAGAAUGACAAU-GUUAUUCUACGAGCGAAGGAUUA	74			
FC50	:	GCAAU--CU-CGGACUAGACUAACGACCUUGGUUUGACGCUA-A	75	*	#	$
FC51	:	GCAAU--CU-CGGACUAGACUAACGACCUUCGUUUGACGCUC-A	76	*	#	$
FC60	:	AGAGCAGCCGGAGGUGUGAGCUCUGACUCUG-AACAGCUG	77	o		
FC76	:	CGGGAUUU--CU-CGGAAAAGACUAACGAC--UAAUUCCAGAACC	78	o		
FCN11	:	GCAAU--CU-CGGACUAGGCUAACGACCUUUGUUUGACGCUC-A	79	*	#	
FCN14	:	GCAAU--CU-CGGACUAGACUAACGACCUUCGUUUGACGCUU-A	80	*	#	$
FCN26	:	UC--CA-AGGACCAAACGGGUGUUCGGCAGUGGACU-UU-AGCAA	81	o	#	
FCN28	:	UGGGCUAC--AU-GUGAGUACACCAGCGUGAGAGUUCUUAGG	82	o	#	
FCN29	:	CUGUGCAGUAACUGCGGAUGAGACCAACCGG-AUGGCUCAAC	83	*	#	
FCN57	:	ACAAU--CU-CGGACUAGACUAACGACCUUCGUUUGACGCUU-A	84	*	#	
FCN61	:	GCAAU--CU-CGGACGAGACUAACGACCUUCGUUUGACGCUU-A	85	*	#	
FCN65	:	AGCGCUAGAUGGACGAGAGACUUUUAAGUAGC-AAGCGGUA	86	*		
score 0.274690						
FC10	:	CAGACUCAGAGCGCCGUGAGCUUCUGAAG-CAA--UCGCAGGU	87	*	#	
FC53	:	G-CGGGGAGCUCCUCGAGAAACUGAGUUCAACUUCCCAGGU	88	o	#	
MOTIF III		score 0.387597				
FC14	:	GUGUUGGAGCUCUUGAUUGGAAAAG--UAGA--ACAAAUCGAAA	89	*	#	$
FC30	:	GUGUUGGAGCUCUUGAUUGGAAAAU--UAGA--GCAAAUCGAAA	90	*	#	$
FC49	:	CAAUCCGAGCUCUUGAA-GCAAUCC--UUGAUUGCAAGAUGAU	91	o		
FC52	:	UCGGAUG-AGCUCUUGAA-GCAGUUC--AAGG--ACAGACAUAAAG	92	*		
FC59	:	UUCCAGGU-UAGCGGCCAAACC--UCGA-CUUGAACAGACUUUA	93	o		
FC70	:	GUGUUGGAGCUCUUGAUUGGAAAAG--UAGA--GCAAAACGAAA	94	*	#	$
FC74	:	GUGUUGGAGCUCUUGAUUGGAAAAG--UAGA--GCAAAUCGAAA	95	*	#	$
FCN2	:	GUGGUGCUGCAAUUGCUCGGUCGGC--GUGCUCUCUACUUGA	96			
FCN3	:	GCUCAAGAGACUGAA-GGAAAAGCUUAGAGCUCAAAGC-AUA	97			
score 0.306520						
FC22	:	CGUGUUGGGUUCAAAGACCAGCUUACGGUACACAGUACGA	98	o		
FCN31	:	UC-UGUUGG-UUCAAAGACUUGCUAAGGGGUCGAAGCACCCU	99	*	/	
score 0.492063						
FC24	:	GAC-GACAAAG-AGUCCGUUC-CAAACCUC-UGAGACAGGGU	100	o		
FCN8	:	U-AGCAAGUCCCACAUCCCAGACGGG-CUAAAAAGAGGUGGA	101	o	%	
FCN18	:	AUGAAC--GACCGCGG--GCAGUCGCGU-UCAAAUGAG-UGGUUUU	102	*	%	
FCN24	:	AUGAGUA-GACCGAGGAAGCACCCGGCUCUCAAAUGAG-UGA	103	*	/	
FCN64	:	AUGAGUA-GACCGAGGAACCACCCGGCUCUCAAAUGAC-UGA	104	o	/	
score 0.294667						
FC25	:	AAGGCC-AU--CAGGGCAAAGACCUCCUAGGUACUGA-CGCUUA	105	o		
FC34	:	AAGGCCGAA--CAACGAAGUUUGAUUC-AGGUACUCAGCG-UUC	106	o	%	

Table 5 (cont'd)

FINAL CLUSTERS		SEQ ID NO	In Vitro Clot Binding	Fibrinogen Affinity	Binding PE Assay
FC35	: AAGGCCGAA--CAACGAAGAUUGAUUC-AGGUACUCAGCG-UUC	107	o		
FCN34	: AAGGCGGAGGGCAAGCAAGA-ACCU-C-ACGAACAGA-CG-UUAA	108	•		
score 0.428395					
FC33	: AGCCUGAGGUAUAGUU---ACG-CU-AUAUGGGA--GGUAGGCUUUA	109	*		
FCN13	: CGUGAUG-ACAGCUCGGACGGCUCAU-UGCGCGGAGUAG-CUA	110	*	%	@
FCN56	: CGGCUCGAUG-CUAGCUGGGACGGCUCAU-UGAGACUGGUUG	111	•	%	
score 0.324074					
FC42	: AGUGCAACCU-GAACCAAACCAAACUAGCGCGCAGUUGGGU	112	o		
FCN36	: AGCAGAUGGUGCUGAGGUAU-CAU-GAAGACGCUGAC-GCUUA	113	•	/	
FCN49	: GAAUGGAGCCAAGAAAGACAGCGAUGUCUCGGAC-GAUGAG	114	o	%	
FCN50	: GAAUGGAGCCAGGAAAGACAGCGAUGUCUCGGAC-GAUGAG	115	*	/	
FCN58	: GGAUGGAGCCAAGAAAGACAGCGAUGUCUCGGAC-GAUGAG	116	o	%	
FCN67	: CGUG-AGAUUCCCCUGCGUAAGACCA-GAAGACUAUCAG-GCU	117			
score 0.335225					
FC43	: AGGGUUGAGGCUUAUCCUUCUUUCGUUCGUGACACGAUCG	118	*		
FCN69	: GAUUGACACGCA--CUCCAAUGGCUC-UGAAGUGUUCGUGUGC	119	•	%	
score 0.296296					
FC46	: AAAUUCAAUGCUCUGAUGGGUUUAUGAGUUAAUGCGU-GGAC	120	o		
FC61	: AAAGGCCCU-UUCAGCAGGGAUC--GAGGUACUGGAU-GGAUA	121	o		
FCN27	: AAAGUCG-UGUGC-GAGAGGCUCA-GAUUUAAUGCGGAGGA	122	o	%	
score 0.343669					
FCN9	: CGUU-GAAAUCGCUCCUCAGU-G-UGAGUUGAAUCAGCUGACC	123	•	%	
FCN21	: AGUUUGGAUUCG-GCAGGUGCUG-AGACUUUGAU-AGCC-ACUA	124	•	%	
FCN22	: GUGAGAAAU-G-UCGGGGGC-GAUGACUUGGA-CGGUCCACCG	125	•	%	
FCN60	: CGUU-GAAAUCGCUCCUCAGC-G-UGAGUUGAAUCAGCUGACC	126			
score 0.376263					
FCN12	: AGAGAGGAACUGCGAUUCAGACCAAAACGGA--AAUGGCUGU	127	•	%	
FCN25	: GAUAUACUAACUUUCUUUGAAAGCCAAAAGUAUUAAUG-CG	128	*	%	
FCN48	: GAUAUACUAACUUUGUUUGAAAGCCAAAAGUAUUAAUG-CG	129	*	/	$
FCN52	: AGCCGAGCUAAUCCCGAAAGUGACCCGGAACGACG-CGGCA	130	o	%	
score 0.363636					

Table 5 KEY

o–low in vitro clot binding
•–moderate in vitro clot binding
*–high in vitro clot binding

%–low fibrinogen affinity, Kd>1mM
/–moderate fibrinogen affinity
#–high fibrinogen affinity, Kd<1mM

@–low binding PE assay
$–high binding PE assay

TABLE 6

Truncation Analysis

		SEQ ID NO:
FC #69	boundary	
	gggagacaagaauaaacgcucaaACAAAUGUGCGCCCUUGGACGAAGUUAACUCGGACGGUUCuucgacaggaggcucacaacaggc	55
69.1(25)	CGAAGUUAACUCGGACGGUUCuucg	131
69.2(29)	CGAAGUUAACUCGGACGGUUCuucgacag	132
69.3(29)	UGGACGAAGUUAACUCGGACGGUUCuucg	133
69.4(41)	CCCUUGGACGAAGUUAACUCGGACGGUUCuucgacaggagg	134
FCN #30	boundary	
	gggagacaagaauaaacgcucaaUAGGAGCCUAGCAGCCCCUGCAUCGAUCACUAGGAUGGUUuucgacaggaggcucacaacaggc	59
N30.1(23)	UCGAUCACUAGGAUGGUUuucga	135
N30.2(30)	UCGAUCACUAGGAUGGUUuucgacaggagg	136
N30.3(31)	CCCCUGCAUCGAUCACUAGGAUGGUUuucga	137
N30.4(38)	CCCCUGCAUCGAUCACUAGGAUGGUUuucgacaggagg	138

```
                      A-C
5'-C-G-A-A-G--U-U-A       U
3'-g-c-u-u-C   G-G-C      C
              UU      A-G G
```

69.1(25)

```
                      C-U
U-C-G-A--U-C-A            A
a-g-c-u   G-G-U           G
       uUU            A-G
```

N30.1(23)

Table 7
Rat Carotid Artery SELEX

Round	Method	Buffer	[2'F-40N8], uM	% bound	Discrimination injured/norm
	Ex Vivo				
1	minced	Ringers lact.	5	6.7	n.a.
2	minced	Ringers lact.	2	2.7	n.a.
3	minced	Ringers lact.	3.4	6.9	n.a.
4	perfused. inj.	Ringers lact.	2.5	0.2	n.a.
5	perfused. inj.	Ringers lact.	5.9	0.6	n.a.
6	perfused. inj.	Ringers lact.	2.3	0.62	n.a.
7	perfused. inj.	Ringers lact.	2.3	0.7	n.a.
8	perf. normal	Ringers lact.	0.75	0.54	
	injured	Ringers lact.	0.75	1.04	1.9
9	perf. normal	PBS	0.75	0.02	
	injured	PBS	0.75	0.07	3.3
10	perf. normal	PBS	0.75	0.1	
	injured	PBS	0.75	0.5	4.5
11	perf. normal	PBS	0.75	0.1	
	injured	PBS	0.75	0.35	3.4
12	perf. normal	PBS	0.75	0.1	
	injured	PBS	0.75	0.34	3.4
	In Vivo		amount injected, nmoles		
13	in vivo	PBS	3	0.01	2.61
40N8(control)	in vivo	PBS	3	n.a.	1.16
14	in vivo	PBS	3	0.02	4.06
15	in vivo	PBS	3.8	0.02	0.94 (not flushed)
15	ex vivo	PBS	3.8 uM	n.a.	4.61
16	in vivo	PBS	3.9	0.005	3.54

Table 8

MOTIF I		FINAL CLUSTERS	SEQ ID NO	INTENSITY OF STAINING	BINDING SPECIFICITY
p3	:	gggagauaaga-auaa-acgcu-caa	139		
p5	:	uucgacaggaggcucacaacaggc	140		
C4	:	ACCA-CUGGGC-CCAG-UUUAG-AAA---CU-CAUU-----GCCCAAAUCCGG	141		
C13	:	AAG--AAGA-AUCG-AAAAAUCUAC--CUUGUUC-GGAGCCUGCUCU	142	+	ns
C15	:	U-CUAG-AC-AG-CGAAGGCUGAGCUAUGACACUGAACUUCUUA	143	-	
C22	:	GCAAUCU-GGA-CUAG-ACUAA-CGAC--CUUCGCU-UGACGCUCA	144		
C26	:	GCAAUCUCGGA-CUAG-ACUAA-CGAC--CUUCGUU-UGACGC--AAU	145		
C33	:	GCAAUCUCGGA-CUAG-ACUAA-CGAC--CUUCGUU-UGACGCUCA	146	++	s
C38	:	GCAAUCUCGGA-CUCG-ACUAA-CGAC--CUUCGUU-UGACGCUCA	147		
C53	:	GACAAUAACCGC------ACCAA-CGUU--CU--GUU-CUUCGCUUGCACGU	148	-	
C57	:	CAAU-UCCCA-CU-G-AUUCG-GGGC--GGUCCUUGCGAUGGCGAGA	149		
C59	:	CUCAGA-CAACCAACAG-CA-C--GUUC-UC-UGUU-UUCGUCGUUUG	150	+++	s
C60	:	GCAAUCUCGGA-CUAG-ACUAA-CGAC--CUUCGUU-UGACGCUUA	151		
C72	:	GCAAUCUCGGA-CUAG-ACUAA-CGAC--CUUCGUU-UGACGCUCG	152		
Civ3	:	CGCU-CAUG-ACCAGGCGCUA-CUGACUG-AGAUGUUGAACUUA	153	-	
Civ14	:	GCAAUCUCGGA-CUAG-ACUAA-CGAC--CCUCGUU-UGACGCUCA	154		
Civ27	:	AUAAGAUCAAC-AUUGG-CG----GUU--UA-UGUUAUUCGUCCGUUUG	155		
Civ30	:	GCAAUCUCGGA-CUAG-ACUAA-CGAC--CUUCGUU-UGACGCUUA	156		
Civ34	:	CACGCGAGAG-CU---UCUAA-AGCU--GCUGAAU-CGA-GCUCCACGA	157		
Civ41	:	ACAAUCUCGGA-CUAG-ACUAA-CGAC--CUUCGUU-UGACGCUUA	158	+++	ns
Civ42	:	GCAAUCUCGGA-UUAG-ACUAA-CGAC--CUUUGUU-UGACGCUCA	159		
Civ48	:	GCAAUCUCGGA-CUAG-ACUAA-CGAC--CUUCGUA-UGACGCUUA	160		
Civ50	:	GCAAUCUCGGA-CUAG-ACUAA-CGAC--CUUCGCU-UGACGCUCA	161		
Civ53	:	GGAGAUCCUCGA-GGAA-ACU---CGAA--CUUCUUCCCGACGUUGA	162		
Civ59	:	ACAGCUCGGA-UAAG-ACUAA-CGAC--CU-AGUU-UG--GCUAAGCAA	163	++	ns
Civ65	:	GCAAUCUCGGA-CUAG-ACUAA-CGAC--CUUCGUU-UGACGCUCA	164		
score 0.268867					
C1	:	ACAAGGGAGUCGGUUUAU-UCAGCCUG-UUCGGAACCUGACU	165	+	ns
C44	:	AUCCAAGACGCUUAGU---UCUUGCUC-UUCGGGGCUUC-CUA-CG	166		
C45	:	AAGUAAACUCGAGACCGUUCUGGCUGAUUCGGGCC-ACUCU	167		
C55	:	ACUUGACAA-UCCCCCUGAUUCGGGGCCUGACUAUCACGA	168	++	ns
C58	:	ACACGACA-UCGAAGUUA-UCCCCCUGAUUCGGAGCCAG-CUG	169	-	

Table 8 (cont'd.)

FINAL CLUSTERS		SEQ ID NO	INTENSITY OF STAINING	BINDING SPECIFICITY
C65	: AGCUGGAAA-UCCAAAUGC-UUUGUCUAGUU-GGGGC--CACUU	170		
C67	: AGACUCUUGAUCA-UCCCCCUAGUUCGGGGC-UGACUG-CACU	171		
Civ6	: ACUUGACAA-UCCCCCUGAUUCGGGGCCUGACUAUCACGAU	172		
Civ24	: GGAGCGAAAUUCUUGAAUA-UCC-ACUGAUUCGGACCGUC-CU	173	-	
Civ29	: GCGGGAUUUUCCUGAUCA-UCCCACUGAUUCGGGGCCUUAG	174		
Civ31	: AGUUUCUCCUUGGCAA-UCCCCCCUAUUCGGGGCUUCAUUG	175		
Civ55	: GAGCGAAAUUCUUGAAUA-UCC-ACUGAUUCGGAGCGUC-CU	176		
Civ56	: ACGGCAUUCUAAACAU-UCCCCCUUGUUCGGAGCCACUCU	177		
Civ62	: GCGGA-UUUUGAUCA-UCCCCCUGAUUCGGAGAC-CUCUUAC178		-	
score 0.286720				
C3	: GGGAACGAAUCGUCCAAAA--GA-CCUCGCGGAAUCGGC-G-UUA	179	+	ns
C17	: GCGAGCUCUU-GCACAAAACCGAUCCUCGC--AUACAGCAGGU	180	-	
C30	: GGGAACGAAUCGUUCAAAA--GA-CCACGCG-AAUCGGC-GCUUA	181		
score 0.441975				
C10	: GAGCUGUUGACGAAAACUUAUGCGGAGAU--GGAUA-CUCGGU	182	+	s
C27	: GAGCUCUUGACGAAAACCUAUUCG-AGAU--GGAUA-CUCGGUU	183		
C35	: GGAGCCGAUUG-UACAACCUAGGUG-AGCU---CAAU-CACCUCGC	184		
C36	: GGGCCCUCUGCUACAACUUCGGCA-AGGA---CAUU-UUCCGGAC	185		
C37	: GAGCUCUUGACGAAAACCUAUGCG-AGAU--GGAUA-CUCGGUU	186	+	ns
C49	: GAAAGC-CAUGUUGAAAGUUUCACCC-AGAUUCGGA---GUCGUUG	187	++	ns
C62	: ACUGAGCUCGUGU--ACAA--UGUUAG-GGAA--GGACAUCUCGAUA	188		
C66	: GAGCUCUUGACGAAAACCUAUGCG-AGAA--GGAUA-CUCGGUU	189		
C69	: GAGCUCUUGACGAAAACCUACGCG-AGAU--GGAAA-CUCGGUU	190		
Civ32	: CACAGGGGUUUC---AAACCUCCCCC-UGAUUCGGAGC-UUC	191		
Civ38	: AACCUCGCCAGGAAUAACU-UGCG-ACUUUCGGAUC-GUCUUA	192	+	ns
Civ54	: GAGCUCUUGACGAAAACCUAUGCG-AGAU--GGAUA-CUCGGUU	193		
Civ64	: CUUUGGAGCUCCUGG----AACGAAAGCG-GAAU---UAAC-UUCCUUA	194		
score 0.303419				
C11	: ACAAUUCAGGACGGGG---UUUCUU---GAAUG--GGUUCGACCUU-CA	195		
C52	: CCAGUA-GAUCAA-CUCCCUGGCAACU---GGUUCGCCGUUAUA	196		
Civ5	: A-CCUUGAUGUUCA--CUCCCU---AACUCAAGGUUCGACGUC-UA	197		
Civ33	: ACAA-CCUGGACAAGGAAUUUUUCU----AGUGUUCGUUGGACGU	198	++	s
Civ35	: A-CCUUGAUGUUGAA-CUCCCU---AACUCAAGGCUCGACGUC-UA	199	++	s

Table 8 (cont'd.)

FINAL CLUSTERS		SEQ ID NO	INTENSITY OF STAINING	BINDING SPECIFICITY
score 0.301361				
C19	: ACGAAGGCAACUUCA-AACAUUUCCUUACGUUCCG-CGCUCA	200		
C51	: ACGGCGCCAACAGCG-AAUGUUCGCCC-CGUUCGGACGCUUA	201		
Civ45	: ACCGACACAACCACG--ACGUUCGGUC-GGUUUGUCCGAUUA	202	+++	s
Civ63	: ACGGAGGCAACCAAG--AGAUUUCCAU-CGUUCGUUCGAUUGA	203		
Civ70	: UCC-AUCCAACGCGGCAAGAUUUGAUG-GACUUUGACGAUCA	204		
score 0.326357				
C23	: AA-GCU--CAGC-AGAUCGGGACUUCUGAUCUUCGGGUCGCUUA	205	-	
Civ67	: CAACGGUAGCGGCUAGAACGCGCCGACUGAU-UUAGG----CUUA	206		
score 0.362963				
C28	: UCCUCCUG-UUCG-GAGUCUCAAUGUCGACUCGGCCGGACCU	207		
Civ12	: AGA-AAUCCCCUUGAUUCG-GAGUCGUCUUUUCGAG-CGUAGU	208	+	ns
Civ26	: AGA-AAUCCCCUUGAUUCG-GAGUCGUCUUUUCGAG-CGAAGG	209		
Civ37	: GAGAGUCAAC-UG---CGAGAAUGG-CUUUCCCAA-CGGCACCUUU	210	+++	s
Civ40	: AGAUAAUCCCCCGGAUUCG-GAGUCCUCUUGACGAA-CUUCC	211		
score 0.356944				
C29	: C-GGA-ACAAACGGAAAUGGCACACAGG-AGAAAGACGAGACC	212		
C34	: CAGGAGAUUAA-GGAACAGGC-CACAGAUAGAGACACG-GAGC	213		
score 0.426357				
C31	: AACUGGACGAGAGGAGCUAGCGUCCAAGUUCGGAGCUA	214	+	ns
Civ44	: ACUGAUUCUCAGCGGCUAGCGCUGAAGUUCG-A-CUAGUUCA	215		
score 0.410853				
C39	: GGCCACAAGCAG-AGAACAGAACAA-CAGAGCGAUGGAG-AGA	216		
C50	: GGAG-CAUCCAGGAUAACAGGCUAAACACCGCAA-GGACCAG	217		
score 0.333333				
C46	: CGGAGGAAGGAAGAGG--AACCUUCGC-CUCUGAUUUAGCUUA	218		
C68	: CGUGGGCAAACUGAGG-CAUUCCCCGCGCUCAGAGAUUCAU	219		
C71	: CAAUGGCAACUAGGCCACAAAGUUC-C-CACUGAUUCGACGU	220		
Civ19	: GCAAUCGGACCGAAAGG----CCUUACC-GAUUUCUCGACCUUUC	221	+++	ns
Civ43	: CGGAGGAAGGAAGAGG--AACCUUUGC-CUCUGAUUUAGCUUA	222		
Civ47	: CGGAGGAAGGAAGAGG--AACCUUCGC-CUCUGAUUUAGCUUA	223		
Civ57	: AGUCGAGUUUCAAGG--AUCAUCCCC-CUCUUCGGAGCCUUUC	224		
Civ58	: CGGAGGAAGGAAGAGG--AGCCUUCGC-CUCUGAUUUAGCUUA	225		

Table 8 (cont'd.)

FINAL CLUSTERS		SEQ ID NO	INTENSITY OF STAINING	BINDING SPECIFICITY
score 0.347884				
C56	: CGAGGCCACCGACAAGGAAGUCG---ACCG-GAGUUGAAGUAAA	226		
Civ39	: GGCC-CCUAGCGGGAUGCCGCUAAUCGCGAAUCGAGGUUUA	227		
score 0.348485				
Civ7	: UCGAUGCU--AUC-GAGUUCU-ACUCGGAAGGUUC-AACGUUUAA	228	++	S
Civ9	: CCCAUACU-GAGA-AAGAACAGACUUCUCAGGUUCGAACGU	229		
Civ13	: CCUGAGACG-GUAC-GAGUUCGGACUC---AGGAUUUAACGCUUU	230		
Civ15	: CUUACUCAACCU-GCGA-ACGCACAG-GUU---AG-UUC-ACCGUUUA	231		
Civ17	: ACCCACACU-GAGA-AAGAACAGACUCCACAGGUUCGAACGU	232		
Civ36	: AAACUCAUUCU-GAGCUAAGCUCA-AGUUC-----UUGCAACGUUUG	233		
Civ49	: ACCGAUUCUCGAAG-CAGCACG--CUCC--AGG-UCUGACGUUUU	234		
Civ66	: ACCUAUACU-GAGA-AAGAACAGACUUCUCAGGUUCGAACGU	235		
score 0.316084				
Civ8	: AGGAACUUAUUCGAC---AUCAG-UCGGUUCCCUGGACGGGUUG	236		
Civ51	: GAACCUAUUCAACCGGAUUAGGUUGGUUCUC-GGAUGUCUA	237		
score 0.439394				

Table 9

<u>Carotid Truncates and Putative Structures</u>

```
                                  A
GA      UC              C        Cu  ga
    CCU   GUUUGAGCU   uc   c
    gga   caaacucgg   ag   a
             c                 g
```

C12.1
(C33 truncate)
(SEQ ID NO: 238)

```
GA      UC              C        A
    CCU   GUUUGAGCUUuucg a
    gga   caaacucggaggac
             c
```

(Civ41 truncate)
(SEQ ID NO: 239)

```
         GUC
CG       G  G         UCGU   A
   UUC        GUUUG    AUUuucga
   gg     a   caaac    uggaggac
                 c        c
```

(Civ45 truncate)
(SEQ ID NO: 240)

```
        G
GUCUUUGuuc
 cggggacag
      a
```

(C59 truncate)
(SEQ ID NO: 241)

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: STEPHENS, ANDREW
SCHNEIDER, DAN
GOLD, LARRY

(ii) TITLE OF INVENTION: NUCLEIC ACID LIGANDS OF TISSUE TARGET

(iii) NUMBER OF SEQUENCES: 241

(iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: Swanson & Bratschun, L.L.C.
(B) STREET: 8400 E. Prentice Avenue, Suite 200
(C) CITY: Englewood
(D) STATE: Colorado
(E) COUNTRY: USA
(F) ZIP: 80111

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Diskette, 3 1/2 diskette, 1.44 MG
(B) COMPUTER: IBM pc compatible
(C) OPERATING SYSTEM: MS-DOS
(D) SOFTWARE: WordPerfect 6.0

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER: PCT/US96/______________
(B) FILING DATE:
(C) CLASSIFICATION:

(vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: 08/433,124
(B) FILING DATE: 03-MAY-1995

(vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: 08/433,126
(B) FILING DATE: 03-MAY-1995

(vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: 07/714,131
(B) FILING DATE: 10-JUNE-1991

(vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: 07/536,428
(B) FILING DATE: 11-JUNE-1990

(vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: 07/964,624
(B) FILING DATE: 21-OCTOBER-1992

(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: Barry J. Swanson
(B) REGISTRATION NUMBER: 33,215
(C) REFERENCE/DOCKET NUMBER: NEX31.2

(ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: (303) 793-3333
(B) TELEFAX: (303) 793-3433

(2) INFORMATION FOR SEQ ID NO:1:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 72 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

```
AGGGAGGACG ATGCGGNNNN NNNNNNNNNN NNNNNNNNNN NNNNNNNNNN     50
NNNNNNCAGA CGACTCGCCC GA                                   72
```

(2) INFORMATION FOR SEQ ID NO:2:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

```
AGGGAGGACG ATGCGG                                          16
```

(2) INFORMATION FOR SEQ ID NO:3:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) FEATURE:
(D) OTHER INFORMATION: N at position 1 represents 3 biotins
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

```
NTCGGGCGAG TCGTCTG                                         17
```

(2) INFORMATION FOR SEQ ID NO:4:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 40 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

```
CCGAAGCTTA ATACGACTCA CTATAGGGAG GACGATGCGG                40
```

(2) INFORMATION FOR SEQ ID NO:5:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:
GCCGGATCCT CGGGCGAGTC GTCTG 25

(2) INFORMATION FOR SEQ ID NO:6:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:
TTCACACAGG AAACAG 16

(2) INFORMATION FOR SEQ ID NO:7:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 71 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:
AGGGAGGACG ATGCGGGGGG TCGGTTCGGG CATATAGGGT ATTCTTCGTA 50
GAGGGCAGAC GACTCGCCCG A 71

(2) INFORMATION FOR SEQ ID NO:8:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 71 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:
AGGGAGGACG ATGCGGGGGG TCGGTTCGGG CATATAGGGT ATTCTTCGTA 50
AAGGGCAGAC GACTCGCCCG A 71

(2) INFORMATION FOR SEQ ID NO:9:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 71 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:
AGGGAGGACG ATGCGGGGGG TCGGTTCGGG CATATAGGGT ATCCTTCGTA 50
GAGGGCAGAC GACTCGCCCG A 71

(2) INFORMATION FOR SEQ ID NO:10:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 72 base pairs
(B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:
AGGGAGGACG ATGCGGCACG TTAGTAGGAT TAGGATTATT CAGGTTGTAG 50
GGAACACAGA CGACTCGCCC GA 72

(2) INFORMATION FOR SEQ ID NO:11:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 74 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:
AGGGAGGACG ATGCGGCACG TTCAGCAGGA TTAGGGTTGT TTNGGTTGTA 50
GGGACACACA GACGACTCGC CCGA 74

(2) INFORMATION FOR SEQ ID NO:12:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 72 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:
AGGGAGGACG ATGCGGCACG GTAGTAAGTA GTAGGGTATT ATAATTAGGG 50
GATCCACAGA CGACTCGCCC GA 72

(2) INFORMATION FOR SEQ ID NO:13:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 72 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:
AGGGAGGACG ATGCGGCACG GCAGTATTAT TCAGGGGTCT TAGATATTAG 50
GGGGCACAGA CGACTCGCCC GA 72

(2) INFORMATION FOR SEQ ID NO:14:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 72 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:
AGGGAGGACG ATGCGGCACG GTAGGTTTTA GATAGGGATA TTTGGTGTAG 50
GGAGCACAGA CGACTCGCCC GA 72

(2) INFORMATION FOR SEQ ID NO:15:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 72 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:
AGGGAGGACG ATGCGGCACG GTAGGTTATA GATAGGGATA TTTNTTGTAG 50
GGAACACAGA CGACTCGCCC GA 72

(2) INFORMATION FOR SEQ ID NO:16:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 72 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:
AGGGAGGACG ATGCGGCACG GTAGGTTTTA GATAGGGATA TTTGATGTAG 50
GGAGCACAGA CGACTCGCCC GA 72

(2) INFORMATION FOR SEQ ID NO:17:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 72 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:
AGGGAGGACG ATGCGGCACG GTAGGTTTTA GATAGGGATA TTTGGTATAG 50
GGAGCACAGA CGACTCGCCC GA 72

(2) INFORMATION FOR SEQ ID NO:18:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 72 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:
AGGGAGGACG ATGCGGCACG GTAGGCTTTA GATAGGGATA TTTGATGTAG 50
GGAGCACAGA CGACTCGCCC GA 72

(2) INFORMATION FOR SEQ ID NO:19:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 72 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:
AGGGAGGACG ATGCGGGGGG AGTAGGGTAT TTAAAAATGT TAGGGTAAGT 50
TTCCTCCAGA CGACTCGCCC GA 72

(2) INFORMATION FOR SEQ ID NO:20:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 72 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:
AGGGAGGACG ATGCGGGGGG AGTAGGGTAT TTAAAAGTGT CAGGGTAAGT 50
TTCCTCCAGA CGACTCGCCC GA 72

(2) INFORMATION FOR SEQ ID NO:21:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 72 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:
AGGGAGGACG ATGCGGCGTA GTAAGAAGTA TTATTAGGGA TATTGTAGGG 50
GCGCTACAGA CGACTCGCCC GA 72

(2) INFORMATION FOR SEQ ID NO:22:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 72 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:
AGGGAGGACG ATGCGGCGTA GTAAGAAGTA TTATTAGGGA TATTGCAGGG 50
GCGCTACAGA CGACTCGCCC GA 72

(2) INFORMATION FOR SEQ ID NO:23:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 71 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:
AGGGAGGACG ATGCGGGGCA GCAAGAGTTT GATTAGGGTA TAGTTAGGGG 50
CGCTGCAGAC GACTCGCCCG A 71

(2) INFORMATION FOR SEQ ID NO:24:
(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 71 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

```
AGGGAGGACG ATGCGGGCAG CAAGAGTTTG ATTAGGGTAT AGTTAGGGGC      50
GCTGCCAGAC GACTCGCCCG A                                     71
```

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 71 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

```
AGGGAGGACG ATGCGGGCAG TAAGGGTTTG ATTAGGGTAT AGTTAGGGGC      50
GCTGCCAGAC GACTCGCCCG A                                     71
```

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 70 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

```
AGGGAGGACG ATGCGGGCAG CAAGAGGTTG ATTAGGGTAT AGTTAGGGGC      50
GCTGCAGACG ACTCGCCCGA                                       70
```

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 72 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

```
AGGGAGGACG ATGCGGCGGC AAGATGATTG AATAGGGGAT CTAAAGTTAG      50
GGGCGCCAGA CGACTCGCCC GA                                    72
```

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 72 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

```
AGGGAGGACG ATGCGGGCAG CAGGTGTAGG GGTATAGATG GATAGGGATT      50
```

TCTTCTCAGA CGACTCGCCC GA 72

(2) INFORMATION FOR SEQ ID NO:29:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 72 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:
AGGGAGGACG ATGCGGCACA TAGGGGAAAT GAGAATAGTA GGGTATTAAT 50
ACAGTGCAGA CGACTCGCCC GA 72

(2) INFORMATION FOR SEQ ID NO:30:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 72 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:
AGGGAGGACG ATGCGGCACA TAGGGGAAAT GAGAAGAATA GGGTATTAAT 50
ACAGTGCAGA CGACTCGCCC GA 72

(2) INFORMATION FOR SEQ ID NO:31:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 72 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:
AGGGAGGACG ATGCGGCAGG TTAGGGGAAA GGTTTAATAA TTAGGGTATA 50
AATGTGCAGA CGACTCGCCC GA 72

(2) INFORMATION FOR SEQ ID NO:32:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 72 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:
AGGGAGGACG ATGCGGCAGG TAGAGATAGG GAAGTTTTAT GTAGGGGACA 50
ATTCGTCAGA CGACTCGCCC GA 72

(2) INFORMATION FOR SEQ ID NO:33:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 72 base pairs
(B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:
AGGGAGGACG ATGCGGCAGG TAGAGATAGG GAAGTTTTAT GTAGGGGACA 50
ATTCGTCAGA CGACTCGCCC GA 72

(2) INFORMATION FOR SEQ ID NO:34:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 72 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:
AGGGAGGACG ATGCGGCACA ATAGGGAAAT TTGTTGTTAT AGTTAGGGAT 50
ACTGGACAGA CGACTCGCCC GA 72

(2) INFORMATION FOR SEQ ID NO:35:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 72 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:
AGGGAGGACG ATGCGGGGCC GAATAGGGAA ATTTATTATT ACTAACAGTA 50
ATCCCCCAGA CGACTCGCCC GA 72

(2) INFORMATION FOR SEQ ID NO:36:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 71 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:
AGGGAGGACG ATGCGGCAGG ACTTAGGGAT TTAGTTGTTT TAGGGGTTAT 50
GTAGTCAGAC GACTCGCCCG A 71

(2) INFORMATION FOR SEQ ID NO:37:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 72 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:
AGGGAGGACG ATGCGGGGGG GGATGAGATG TAATCCACAT GTCACTTATT 50
AAGTCCCAGA CGACTCGCCC GA 72

(2) INFORMATION FOR SEQ ID NO:38:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 72 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

AGGGAGGACG ATGCGGCAGG GGATGGGATG TAATCCTCAT GTCACTTATT 50
AAGTCCCAGA CGACTCGCCC GA 72

(2) INFORMATION FOR SEQ ID NO:39:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 72 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

AGGGAGGACG ATGCGGTACG ACTACGATTG AGTATCCGGC TATAATATTA 50
CCATTGCAGA CGACTCGCCC GA 72

(2) INFORMATION FOR SEQ ID NO:40:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

GGGAGAUAAG AAUAAACGCU CAANNNNNNN NNNNNNNNNN NNNNNNNNNN 50
NNNNNNNNNN NNNUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:41:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 40 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

TAATACGACT CACTATAGGG AGAUAAGAAU AAACGCUCAA 40

(2) INFORMATION FOR SEQ ID NO:42:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:
GCCTGTTGTG AGCCTCCTGT CGAA 24

(2) INFORMATION FOR SEQ ID NO:43:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:
GGGAGAUAAG AAUAAACGCU CAAAGGGCUC GUGUGCCAAA UCGCUAACAA 50
CAAGCUAGCU GAUUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:44:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:
GGGAGAUAAG AAUAAACGCU CAACUGGGCU CAUCCGGCGA AUGAUGCAAG 50
GAAGAUUUCA CAUUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:45:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:
GGGAGAUAAG AAUAAACGCU CAAAAGGAUA GUGUGCUCCU GUACCAAAUU 50

UCCAAAGCGA UAUUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:46:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:
GGGAGAUAAG AAUAAACGCU CAAAAAGAGU AAAGCGCGGA ACAGGAUUCA 50
CGUUGCGCUC UUUUCGACAG GAGGCUCACA ACAGGC 86

(2) INFORMATION FOR SEQ ID NO:47:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 85 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:
GGGAGAUAAG AAUAAACGCU CAAAAAGAGU AAAGCGCGGA ACAGGAUUCA 50
CGUUGCGCUC AUUCGACAGG AGGCUCACAA CAGGC 85

(2) INFORMATION FOR SEQ ID NO:48:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:
GGGAGAUAAG AAUAAACGCU CAACAACGAU UAUCUUUUCG GCCGUGAAAC 50
CCAAACUGAC GCCUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:49:
(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

GGGAGAUAAG AAUAAACGCU CAACGCGAGG AUAGGGUGCA GCUUCUGUUC 50
CAAAUACGUG AAUUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:50:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

GGGAGAUAAG AAUAAACGCU CAAUAAGUCG AAGAGCUCCU GAUCCAAACC 50
AUCGAAAGGA CGUUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:51:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

GGGAGAUAAG AAUAAACGCU CAAGGUAAGU UGGAGCUCCU UAUCCAAGCA 50
CGCAAUAAGU GACUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:52:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

```
GGGAGAUAAG AAUAAACGCU CAAUUUGGCG UGGGAUCCUG GACUGAAGGA      50
UUUUGACGAU GCUUCGACAG GAGGCUCACA ACAGGC                    86
```

(2) INFORMATION FOR SEQ ID NO:53:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

```
GGGAGAUAAG AAUAAACGCU CAAAUUCAAG ACAGAGACUU UCCUUGAAUG      50
CUCUGUCCCA UAAUUCGACA GGAGGCUCAC AACAGGC                   87
```

(2) INFORMATION FOR SEQ ID NO:54:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

```
GGGAGAUAAG AAUAAACGCU CAAACAAAUG UGCGACCUUG GACGAAGUUA      50
ACUCGGACGG UUCUUCGACA GGAGGCUCAC AACAGGC                   87
```

(2) INFORMATION FOR SEQ ID NO:55:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

GGGAGAUAAG AAUAAACGCU CAAACAAAUG UGCGCCCUUG GACGAAGUUA 50
ACUCGGACGG UUCUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: All C's are 2'-F cytosine

(ix) FEATURE:

(D) OTHER INFORMATION: All U's are 2'-F uracil

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

GGGAGAUAAG AAUAAACGCU CAAACAAAUG UGCGCCCUUG GACGAAGUUA 50
ACUCGGACGG UUGUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: All C's are 2'-F cytosine

(ix) FEATURE:

(D) OTHER INFORMATION: All U's are 2'-F uracil

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

GGGAGAUAAG AAUAAACGCU CAAACAAAUG UGCGCCCUUG GACGAAGUUA 50
ACUCGGACGG UUCUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:58:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: All C's are 2'-F cytosine

(ix) FEATURE:

(D) OTHER INFORMATION: All U's are 2'-F uracil

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

GGGAGAUAAG AAUAAACGCU CAAAAGUCUG AGACUCCUGG ACUGAAUUAG 50
CUAGGACGGC UGUUCGACAG GAGGCUCACA ACAGGC 86

(2) INFORMATION FOR SEQ ID NO:59:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:
GGGAGAUAAG AAUAAACGCU CAAUAGGAGC CUAGCAGCCC CUGCAUCGAU 50
CACUAGGAUG GUUUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:60:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:
GGGAGAUAAG AAUAAACGCU CAAAAAGUGU AGCCUUCCUG GACUGUAGGU 50
ACUAGGACGG UCCUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:61:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 83 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:
GGGAGAUAAG AAUAAACGCU CAAACAAAUG UGCUCCCUUG GACGAAGUUA 50
ACUCGGCGGU UCGACAGGAG GCUCACAACA GGC 83

(2) INFORMATION FOR SEQ ID NO:62:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:
GGGAGAUAAG AAUAAACGCU CAAAAGAAGC UGGCGACAGG CGAAAAGCAG 50
ACUUGAGGGG AAUUCGACAG GAGGCUCACA ACAGGC 86

(2) INFORMATION FOR SEQ ID NO:63:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:
GGGAGAUAAG AAUAAACGCU CAAAGUAGGU GAGGCUUCUG GACUGAAGUA 50
ACUAGGUCGG UUCUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:64:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:
GGGAGAUAAG AAUAAACGCU CAACAUGAGC UGCUGGACCA AACAGAUGGA 50
GGAACCACCG UGUUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:65:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine

(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:
GGGAGAUAAG AAUAAACGCU CAAGAGCUCU UGACGAAAAC CUAUGCGAGA 50
UGGAUACUCG GUUUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:66:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:
GGGAGAUAAG AAUAAACGCU CAAGAGCUCU UGACGAAAAC CUAUGCGAGA 50
AGGAUACUCG GUUUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:67:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 85 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:
GGGAGAUAAG AAUAAACGCU CAAGAGCUCU AGACGAAAAC CUAUGCGAGA 50
UGAUACUCGG UCUUCGACAG GAGGCUCAAA CAGGC 85

(2) INFORMATION FOR SEQ ID NO:68:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 88 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:
GGGAGAUAAG AAUAAACGCU CAAUGAGCUC UUGAAGAAGU CCGAACAUUC 50

UCCUUUCUGC GACUUUCGAC AGGAGGCUCA CAACAGGC 88

(2) INFORMATION FOR SEQ ID NO:69:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:
GGGAGAUAAG AAUAAACGCU CAAGAGCUCC GGGAUCCAAG CGUGCAACAA 50
CACUAUGCCC ACUUCGACAG GAGGCUCACA ACAGGC 86

(2) INFORMATION FOR SEQ ID NO:70:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:
GGGAGAUAAG AAUAAACGCU CAAAAUACCC UCGGGAACCA AUCCGACCCU 50
AUUUUGCAGU UUGUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:71:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:
GGGAGAUAAG AAUAAACGCU CAAAUGAUGC UCCUGAAGUA AUCACCAGGA 50
CAUCCUCGGC AUUUCGACAG GAGGCUCACA ACAGGC 86

(2) INFORMATION FOR SEQ ID NO:72:
(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:

GGGAGAUAAG AAUAAACGCU CAAGCAAUCU CGGACUAGAC CAACGACCUU 50
CGUUUGACGC UCAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:73:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:73:

GGGAGAUAAG AAUAAACGCU CAACCGAUUU CUAGGACGGA UUUACGGAGA 50
AUUGAGUCGC AAGUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:74:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:74:

GGGAGAUAAG AAUAAACGCU CAAACGGCGA GAAUGACAAU GUUAUUCUAC 50
GAGCGAAGGA UUAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:75:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:75:

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GGGAGAUAAG AAUAAACGCU CAAGCAAUCU CGGACUAGAC UAACGACCUU     50
GGUUUGACGC UAAUUCGACA GGAGGCUCAC AACAGGC                   87
```

(2) INFORMATION FOR SEQ ID NO:76:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:76:

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GGGAGAUAAG AAUAAACGCU CAAGCAAUCU CGGACUAGAC UAACGACCUU     50
CGUUUGACGC UCAUUCGACA GGAGGCUCAC AACAGGC                   87
```

(2) INFORMATION FOR SEQ ID NO:77:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

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GGGAGAUAAG AAUAAACGCU CAAAGAGCAG CCGGAGGUGU GAGCUCUGAC     50
UCUGAACAGC UGUUCGACAG GAGGCUCACA ACAGGC                    86
```

(2) INFORMATION FOR SEQ ID NO:78:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:78:

GGGAGAUAAG AAUAAACGCU CAACGGGAUU UCUCGGAAAA GACUAACGAC 50
UAAUUCCAGA ACCUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:79:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: All C's are 2'-F cytosine

(ix) FEATURE:

(D) OTHER INFORMATION: All U's are 2'-F uracil

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:79:

GGGAGAUAAG AAUAAACGCU CAAGCAAUCU CGGACUAGGC UAACGACCUU 50
UGUUUGACGC UCAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:80:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: All C's are 2'-F cytosine

(ix) FEATURE:

(D) OTHER INFORMATION: All U's are 2'-F uracil

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:80:

GGGAGAUAAG AAUAAACGCU CAAGCAAUCU CGGACUAGAC UAACGACCUU 50
CGUUUGACGC UUAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:81:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: All C's are 2'-F cytosine

(ix) FEATURE:

(D) OTHER INFORMATION: All U's are 2'-F uracil

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:81:

GGGAGAUAAG AAUAAACGCU CAAUCCAAGG ACCAAACGGG UGUUCGGCAG 50
UGGACUUUAG CAAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:82:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 86 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: All C's are 2'-F cytosine

(ix) FEATURE:

(D) OTHER INFORMATION: All U's are 2'-F uracil

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:

GGGAGAUAAG AAUAAACGCU CAAUGGGCUA CAUGUGAGUA CACCAGCGUG 50
AGAGUUCUUA GGUUCGACAG GAGGCUCACA ACAGGC 86

(2) INFORMATION FOR SEQ ID NO:83:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 88 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: All C's are 2'-F cytosine

(ix) FEATURE:

(D) OTHER INFORMATION: All U's are 2'-F uracil

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:

GGGAGAUAAG AAUAAACGCU CAACUGUGCA GUAACUGCGG AUGAGACCAA 50
CCGGAUGGCU CAACUUCGAC AGGAGGCUCA CAACAGGC 88

(2) INFORMATION FOR SEQ ID NO:84:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 87 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: All C's are 2'-F cytosine

(ix) FEATURE:

(D) OTHER INFORMATION: All U's are 2'-F uracil

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:84:

GGGAGAUAAG AAUAAACGCU CAAACAAUCU CGGACUAGAC UAACGACCUU 50
CGUUUGACGC UUAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:85:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 87 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:

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GGGAGAUAAG AAUAAACGCU CAAGCAAUCU CGGACGAGAC UAACGACCUU     50
CGUUUGACGC UUAUUCGACA GGAGGCUCAC AACAGGC                   87
```

(2) INFORMATION FOR SEQ ID NO:86:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:

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GGGAGAUAAG AAUAAACGCU CAAAGCGCUA GAUGGACGAG AGACUUUUAA     50
GUAGCAAGCG GUAUUCGACA GGAGGCUCAC AACAGGC                   87
```

(2) INFORMATION FOR SEQ ID NO:87:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:

```
GGGAGAUAAG AAUAAACGCU CAACAGACUC AGAGCGCCGU GAGCUUCUGA     50
AGCAAUCGCA GGUUUCGACA GGAGGCUCAC AACAGGC                   87
```

(2) INFORMATION FOR SEQ ID NO:88:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine

(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:
GGGAGAUAAG AAUAAACGCU CAAGCGGGGA GCUCCUCGAG AAACUGAGUU 50
CAACUUCCCA GGUUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:89:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:89:
GGGAGAUAAG AAUAAACGCU CAAGUGUUGG AGCUCUUGAU UGGAAAAGUA 50
GAACAAAUCG AAAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:90:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:
GGGAGAUAAG AAUAAACGCU CAAGUGUUGG AGCUCUUGAU UGGAAAAUUA 50
GAGCAAAUCG AAAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:91:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:91:
GGGAGAUAAG AAUAAACGCU CAACAAUCCG AGCUCUUGAA GCAAUCCUUG 50

AUUGCAAGAU GAUUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:92:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 87 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: All C's are 2'-F cytosine

(ix) FEATURE:

(D) OTHER INFORMATION: All U's are 2'-F uracil

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:

GGGAGAUAAG AAUAAACGCU CAAUCGGAUG AGCUCUUGAA GCAGUUCAAG 50
GACAGACAUA AAGUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:93:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 87 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: All C's are 2'-F cytosine

(ix) FEATURE:

(D) OTHER INFORMATION: All U's are 2'-F uracil

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:

GGGAGAUAAG AAUAAACGCU CAAUUCCAGG UUAGCGGCCA AACCUCGACU 50
UGAACAGACU UUAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:94:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 87 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: All C's are 2'-F cytosine

(ix) FEATURE:

(D) OTHER INFORMATION: All U's are 2'-F uracil

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:94:

GGGAGAUAAG AAUAAACGCU CAAGUGUUGG AGCUCUUGAU UGGAAAAGUA 50
GAGCAAAACG AAAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:95:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:95:

GGGAGAUAAG AAUAAACGCU CAAGUGUUGG AGCUCUUGAU UGGAAAAGUA 50
GAGCAAAUCG AAAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:96:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:96:

GGGAGAUAAG AAUAAACGCU CAAGUGGUGC UGCAAUUGCU CGGUCGGCGU 50
GCUCUCUACU UGAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:97:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:97:

GGGAGAUAAG AAUAAACGCU CAAGCUCAAG AGACUGAAGG AAAAGCUUAG 50
AGCUCAAAGC AUAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:98:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:98:

GGGAGAUAAG AAUAAACGCU CAACGUGUUG GGUUCAAAGA CCAGCUUACG 50
GUACACAGUA CGAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:99:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:99:

GGGAGAUAAG AAUAAACGCU CAAUCUGUUG GUUCAAAGAC UUGCUAAGGG 50
GUCGAAGCAC CCUUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:100:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 85 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:100:

GGGAGAUAAG AAUAAACGCU CAAGACGACA AAGAGUCCGU UCCAAACCUC 50
UGAGACAGGG UUUCGACAGG AGGCUCACAA CAGGC 85

(2) INFORMATION FOR SEQ ID NO:101:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:101:
GGGAGAUAAG AAUAAACGCU CAAUAGCAAG UCCCACAUCC CAGACGGGCU 50
AAAAAGAGGU GGAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:102:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:102:
GGGAGAUAAG AAUAAACGCU CAAAUGAACG ACCGCGGGCA GUCGCGUUCA 50
AAUGAGUGGU UUUUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:103:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:103:
GGGAGAUAAG AAUAAACGCU CAAAUGAGUA GACCGAGGAA GCACCCGGCU 50
CUCAAAUGAG UGAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:104:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:104:
GGGAGAUAAG AAUAAACGCU CAAAUGAGUA GACCGAGGAA GCACCCGGCU 50
CUCAAAUGAC UGAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:105:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:105:
GGGAGAUAAG AAUAAACGCU CAAAAGGCCA UCAGGGCAAA GACCUCCUAG 50
GUACUGACGC UUAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:106:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:106:
GGGAGAUAAG AAUAAACGCU CAAAAGGCCG AACAACGAAG UUUGAUUCAG 50
GUACUCAGCG UUCUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:107:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:107:
GGGAGAUAAG AAUAAACGCU CAAAAGGCCG AACAACGAAG AUUGAUUCAG 50
GUACUCAGCG UUCUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:108:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:108:

GGGAGAUAAG AAUAAACGCU CAAAAGGCGG AGGGCAAGCA AGAACCUCAC 50
GAACAGACGU UAAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:109:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:109:

GGGAGAUAAG AAUAAACGCU CAAAGCCUGA GGUAUAGUUA CGCUAUAUGG 50
GAGGUAGGCU UUAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:110:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:110:

GGGAGAUAAG AAUAAACGCU CAACGUGAUG ACAGCUCGGA CGGCUCAUUG 50
CGCGGAGUAG CUAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:111:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine

(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:111:
GGGAGAUAAG AAUAAACGCU CAACGGCUCG AUGCUAGCUG GGACGGCUCA 50
UUGAGACUGG UUGUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:112:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:112:
GGGAGAUAAG AAUAAACGCU CAAAGUGCAA CCUGAACCAA ACCAAACUAG 50
CGCGCAGUUG GGUUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:113:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:113:
GGGAGAUAAG AAUAAACGCU CAAAGCAGAU GGUGCUGAGG UAUCAUGAAG 50
ACGCUGACGC UUAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:114:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:114:
GGGAGAUAAG AAUAAACGCU CAAGAAUGGA GCCAAGAAAG ACAGCGAUGU 50

CUCGGACGAU GAGUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:115:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:115:
GGGAGAUAAG AAUAAACGCU CAAGAAUGGA GCCAGGAAAG ACAGCGAUGU 50
CUCGGACGAU GAGUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:116:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:116:
GGGAGAUAAG AAUAAACGCU CAAGGAUGGA GCCAAGAAAG ACAGCGAUGU 50
CUCGGACGAU GAGUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:117:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:117:
GGGAGAUAAG AAUAAACGCU CAACGUGAGA UUCCCCUGCG UAAGACCAGA 50
AGACUAUCAG GCUUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:118:
(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:118:

GGGAGAUAAG AAUAAACGCU CAAAGGGUUG AGGCUUAUCC UUCUUUCGUU 50
CGUGACACGA UCGUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:119:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:119:

GGGAGAUAAG AAUAAACGCU CAAGAUUGAC ACGCACUCCA AUGGCUCUGA 50
AGUGUUCGUG UGCUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:120:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 88 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:120:

GGGAGAUAAG AAUAAACGCU CAAAAAUUCA AUGCUCUGAU GGGUUUAUGA 50
GUUAAUGCGU GGACUUCGAC AGGAGGCUCA CAACAGGC 88

(2) INFORMATION FOR SEQ ID NO:121:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:121:

GGGAGAUAAG AAUAAACGCU CAAAAAGGCC CUUUCAGCAG GGAUCGAGGU 50
ACUGGAUGGA UAUUCGACAG GAGGCUCACA ACAGGC 86

(2) INFORMATION FOR SEQ ID NO:122:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 85 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:122:

GGGAGAUAAG AAUAAACGCU CAAAAAGUCG UGUGCGAGAG GCUCAGAUUU 50
AAUGCGGAGG AUUCGACAGG AGGCUCACAA CAGGC 85

(2) INFORMATION FOR SEQ ID NO:123:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:123:

GGGAGAUAAG AAUAAACGCU CAACGUUGAA AUCGCUCCUC AGUGUGAGUU 50
GAAUCAGCUG ACCUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:124:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:124:

GGGAGAUAAG AAUAAACGCU CAAAGUUUGG AUUCGGCAGG UGCUGAGACU 50
UUGAUAGCCA CUAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:125:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: All C's are 2'-F cytosine

(ix) FEATURE:

(D) OTHER INFORMATION: All U's are 2'-F uracil

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:125:

GGGAGAUAAG AAUAAACGCU CAAGUGAGAA AUGUCGGGGG CGAUGACUUG 50
GACGGUCCAC CGUUCGACAG GAGGCUCACA ACAGGC 86

(2) INFORMATION FOR SEQ ID NO:126:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: All C's are 2'-F cytosine

(ix) FEATURE:

(D) OTHER INFORMATION: All U's are 2'-F uracil

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:126:

GGGAGAUAAG AAUAAACGCU CAACGUUGAA AUCGCUCCUC AGCGUGAGUU 50
GAAUCAGCUG ACCUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:127:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: All C's are 2'-F cytosine

(ix) FEATURE:

(D) OTHER INFORMATION: All U's are 2'-F uracil

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:127:

GGGAGAUAAG AAUAAACGCU CAAAGAGAGG AACUGCGAUU CAGACCAAAA 50
CGGAAAUGGC UGUUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:128:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 87 base pairs
        (B) TYPE: nucleic acid
        (C) STRANDEDNESS: single
        (D) TOPOLOGY: linear
    (ix) FEATURE:
        (D) OTHER INFORMATION: All C's are 2'-F cytosine
    (ix) FEATURE:
        (D) OTHER INFORMATION: All U's are 2'-F uracil
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:128:
GGGAGAUAAG AAUAAACGCU CAAGAUAUAC UAACUUUCUU UGAAAGCCAA 50
AAGUAUUAAU GCGUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:129:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 87 base pairs
        (B) TYPE: nucleic acid
        (C) STRANDEDNESS: single
        (D) TOPOLOGY: linear
    (ix) FEATURE:
        (D) OTHER INFORMATION: All C's are 2'-F cytosine
    (ix) FEATURE:
        (D) OTHER INFORMATION: All U's are 2'-F uracil
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:129:
GGGAGAUAAG AAUAAACGCU CAAGAUAUAC UAACUUUGUU UGAAAGCCAA 50
AAGUAUUAAU GCGUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:130:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 87 base pairs
        (B) TYPE: nucleic acid
        (C) STRANDEDNESS: single
        (D) TOPOLOGY: linear
    (ix) FEATURE:
        (D) OTHER INFORMATION: All C's are 2'-F cytosine
    (ix) FEATURE:
        (D) OTHER INFORMATION: All U's are 2'-F uracil
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:130:
GGGAGAUAAG AAUAAACGCU CAAAGCCGAG CUAAUCCCGA AAGUGACCCG 50
GAACGACGCG GCAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:131:
    (i) SEQUENCE CHARACTERISTICS:
        (A) LENGTH: 25 base pairs
        (B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:131:
CGAAGUUAAC UCGGACGGUU CUUCG 25

(2) INFORMATION FOR SEQ ID NO:132:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:132:
CGAAGUUAAC UCGGACGGUU CUUCGACAG 29

(2) INFORMATION FOR SEQ ID NO:133:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:133:
UGGACGAAGU UAACUCGGAC GGUUCUUCG 29

(2) INFORMATION FOR SEQ ID NO:134:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 41 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:134:

CCCUUGGACG AAGUUAACUC GGACGGUUCU UCGACAGGAG G 41

(2) INFORMATION FOR SEQ ID NO:135:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:135:
UCGAUCACUA GGAUGGUUUU CGA 23

(2) INFORMATION FOR SEQ ID NO:136:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:136:
UCGAUCACUA GGAUGGUUUU CGACAGGAGG 30

(2) INFORMATION FOR SEQ ID NO:137:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 31 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:137:
CCCCUGCAUC GAUCACUAGG AUGGUUUUCG A 31

(2) INFORMATION FOR SEQ ID NO:138:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 38 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:138:
CCCCUGCAUC GAUCACUAGG AUGGUUUUCG ACAGGAGG 38

(2) INFORMATION FOR SEQ ID NO:139:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:139:
GGGAGAUAAG AAUAAACGCU CAA 23

(2) INFORMATION FOR SEQ ID NO:140:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:140:
UUCGACAGGA GGCUCACAAC AGGC 24

(2) INFORMATION FOR SEQ ID NO:141:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:141:
GGGAGAUAAG AAUAAACGCU CAAACCACUG GGCCCAGUUU AGAAACUCAU 50
UGCCCAAAUC CGGUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:142:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 87 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: All C's are 2'-F cytosine

(ix) FEATURE:

(D) OTHER INFORMATION: All U's are 2'-F uracil

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:142:

GGGAGAUAAG AAUAAACGCU CAAAAGAAGA AUCGAAAAAU CUACCUUGUU 50
CGGAGCCUGC UCUUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:143:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 87 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: All C's are 2'-F cytosine

(ix) FEATURE:

(D) OTHER INFORMATION: All U's are 2'-F uracil

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:143:

GGGAGAUAAG AAUAAACGCU CAAUCUAGAC AGCGAAGGCU GAGCUAUGAC 50
ACUGAACUUC UUAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:144:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 86 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: All C's are 2'-F cytosine

(ix) FEATURE:

(D) OTHER INFORMATION: All U's are 2'-F uracil

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:144:

GGGAGAUAAG AAUAAACGCU CAAGCAAUCU GGACUAGACU AACGACCUUC 50
GCUUGACGCU CAUUCGACAG GAGGCUCACA ACAGGC 86

(2) INFORMATION FOR SEQ ID NO:145:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 87 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:145:

GGGAGAUAAG AAUAAACGCU CAAGCAAUCU CGGACUAGAC UAACGACCUU 50
CGUUUGACGC AAUUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:146:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:146:

GGGAGAUAAG AAUAAACGCU CAAGCAAUCU CGGACUAGAC UAACGACCUU 50
CGUUUGACGC UCAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:147:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:147:

GGGAGAUAAG AAUAAACGCU CAAGCAAUCU CGGACUCGAC UAACGACCUU 50
CGUUUGACGC UCAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:148:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine

(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:148:
GGGAGAUAAG AAUAAACGCU CAAGACAAUA ACCGCACCAA CGUUCUGUUC 50
UUCGCUUGCA CGUUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:149:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:149:
GGGAGAUAAG AAUAAACGCU CAACAAUUCC CACUGAUUCG GGGCGGUCCU 50
UGCGAUGGCG AGAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:150:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:150:
GGGAGAUAAG AAUAAACGCU CAACUCAGAC AACCAACAGC ACGUUCUCUG 50
UUUUCGUCGU UUGUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:151:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:151:
GGGAGAUAAG AAUAAACGCU CAAGCAAUCU CGGACUAGAC UAACGACCUU 50

CGUUUGACGC UUAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:152:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:152:
GGGAGAUAAG AAUAAACGCU CAAGCAAUCU CGGACUAGAC UAACGACCUU 50
CGUUUGACGC UCGUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:153:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:153:
GGGAGAUAAG AAUAAACGCU CAACGCUCAU GACCAGGCGC UACUGACUGA 50
GAUGUUGAAC UUAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:154:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:154:
GGGAGAUAAG AAUAAACGCU CAAGCAAUCU CGGACUAGAC UAACGACCCU 50
CGUUUGACGC UCAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:155:
(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:155:

GGGAGAUAAG AAUAAACGCU CAAAUAAGAU CAACAUUGGC GGUUUAUGUU 50
AUUCGUCCGU UUGUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:156:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:156:

GGGAGAUAAG AAUAAACGCU CAAGCAAUCU CGGACUAGAC UAACGACCUU 50
CGUUUGACGC UUAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:157:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:157:

GGGAGAUAAG AAUAAACGCU CAACACGCGA GAGCUUCUAA AGCUGCUGAA 50
UCGAGCUCCA CGAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:158:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:158:

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GGGAGAUAAG AAUAAACGCU CAAACAAUCU CGGACUAGAC UAACGACCUU    50
CGUUUGACGC UUAUUCGACA GGAGGCUCAC AACAGGC                  87
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(2) INFORMATION FOR SEQ ID NO:159:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:159:

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GGGAGAUAAG AAUAAACGCU CAAGCAAUCU CGGAUUAGAC UAACGACCUU    50
UGUUUGACGC UCAUUCGACA GGAGGCUCAC AACAGGC                  87
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(2) INFORMATION FOR SEQ ID NO:160:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:160:

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GGGAGAUAAG AAUAAACGCU CAAGCAAUCU CGGACUAGAC UAACGACCUU    50
CGUAUGACGC UUAUUCGACA GGAGGCUCAC AACAGGC                  87
```

(2) INFORMATION FOR SEQ ID NO:161:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:161:
GGGAGAUAAG AAUAAACGCU CAAGCAAUCU CGGACUAGAC UAACGACCUU 50
CGCUUGACGC UCAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:162:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:162:
GGGAGAUAAG AAUAAACGCU CAAGGAGAUC CUCGAGGAAA CUCGAACUUC 50
UUCCCGACGU UGAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:163:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:163:
GGGAGAUAAG AAUAAACGCU CAAACAGCUC GGAUAAGACU AACGACCUAG 50
UUUGGCUAAG CAAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:164:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:164:
GGGAGAUAAG AAUAAACGCU CAAGCAAUCU CGGACUAGAC UAACGACCUU 50
CGUUUGACGC UCAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:165:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:165:
GGGAGAUAAG AAUAAACGCU CAAACAAGGG AGUCGGUUUA UUCAGCCUGU 50
UCGGAACCUG ACUUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:166:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:166:
GGGAGAUAAG AAUAAACGCU CAAAUCCAAG ACGCUUAGUU CUUGCUCUUC 50
GGGGCUUCCU ACGUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:167:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:167:
GGGAGAUAAG AAUAAACGCU CAAAAGUAAA CUCGAGACCG UUCUGGCUGA 50
UUCGGGGCAC UCUUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:168:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:168:

GGGAGAUAAG AAUAAACGCU CAAACUUGAC AAUCCCCCUG AUUCGGGGCC 50
UGACUAUCAC GAUUCGACAG GAGGCUCACA ACAGGC 86

(2) INFORMATION FOR SEQ ID NO:169:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:169:

GGGAGAUAAG AAUAAACGCU CAAACACGAC AUCGAAGUUA UCCCCCUGAU 50
UCGGAGCCAG CUGUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:170:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:170:

GGGAGAUAAG AAUAAACGCU CAAAGCUGGA AAUCCAAAUG CUUUGUCUAG 50
UUGGGGCCAC UUUUCGACAG GAGGCUCACA ACAGGC 86

(2) INFORMATION FOR SEQ ID NO:171:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine

(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:171:
GGGAGAUAAG AAUAAACGCU CAAAGACUCU UGAUCAUCCC CCUAGUUCGG 50
GGCUGACUGC ACUUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:172:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:172:
GGGAGAUAAG AAUAAACGCU CAAACUUGAC AAUCCCCCUG AUUCGGGGCC 50
UGACUAUCAC GAUUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:173:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:173:
GGGAGAUAAG AAUAAACGCU CAAGGAGCGA AAUUCUUGAA UAUCCACUGA 50
UUCGGACCGU CCUUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:174:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:174:
GGGAGAUAAG AAUAAACGCU CAAGCGGGAU UUUCCUGAUC AUCCCACUGA 50

UUCGGGGCCU UAGUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:175:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:175:
GGGAGAUAAG AAUAAACGCU CAAAGUUUCU CCUUGGCAAU CCCCCCUAUU 50
CGGGGCUUCA UUGUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:176:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:176:
GGGAGAUAAG AAUAAACGCU CAAGAGCGAA AUUCUUGAAU AUCCACUGAU 50
UCGGAGCGUC CUUUCGACAG GAGGCUCACA ACAGGC 86

(2) INFORMATION FOR SEQ ID NO:177:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:177:
GGGAGAUAAG AAUAAACGCU CAAACGGCAU UCUAAACAUU CCCCCUUGUU 50
CGGAGCCACU CUUUCGACAG GAGGCUCACA ACAGGC 86

(2) INFORMATION FOR SEQ ID NO:178:
(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:178:

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GGGAGAUAAG AAUAAACGCU CAAGCGGAUU UUGAUCAUCC CCCUGAUUCG      50
GAGACCUCUU ACUUCGACAG GAGGCUCACA ACAGGC                     86
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(2) INFORMATION FOR SEQ ID NO:179:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:179:

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GGGAGAUAAG AAUAAACGCU CAAGGGAACG AAUCGUCCAA AAGACCUCGC      50
GGAAUCGGCG UUAUUCGACA GGAGGCUCAC AACAGGC                    87
```

(2) INFORMATION FOR SEQ ID NO:180:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:180:

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GGGAGAUAAG AAUAAACGCU CAAGCGAGCU CUUGCACAAA ACCGAUCCUC      50
GCAUACAGCA GGUUUCGACA GGAGGCUCAC AACAGGC                    87
```

(2) INFORMATION FOR SEQ ID NO:181:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:181:
GGGAGAUAAG AAUAAACGCU CAAGGGAACG AAUCGUUCAA AAGACCACGC 50
GAAUCGGCGC UUAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:182:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:182:
GGGAGAUAAG AAUAAACGCU CAAGAGCUGU UGACGAAAAC UUAUGCGGAG 50
AUGGAUACUC GGUUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:183:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:183:
GGGAGAUAAG AAUAAACGCU CAAGAGCUCU UGACGAAAAC CUAUUCGAGA 50
UGGAUACUCG GUUUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:184:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:184:
GGGAGAUAAG AAUAAACGCU CAAGGAGCCG AUUGUACAAC CUAGGUGAGC 50
UCAAUCACCU CGCUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:185:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:185:
GGGAGAUAAG AAUAAACGCU CAAGGGCCCU CUGCUACAAC UUCGGCAAGG 50
ACAUUUUCCG GACUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:186:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:186:
GGGAGAUAAG AAUAAACGCU CAAGAGCUCU UGACGAAAAC CUAUGCGAGA 50
UGGAUACUCG GUUUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:187:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 88 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:187:
GGGAGAUAAG AAUAAACGCU CAAGAAAGCC AUGUUGAAAG UUUCACCCAG 50
AUUCGGAGUC GUUGUUCGAC AGGAGGCUCA CAACAGGC 88

(2) INFORMATION FOR SEQ ID NO:188:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:188:
GGGAGAUAAG AAUAAACGCU CAAACUGAGC UCGUGUACAA UGUUAGGGAA 50
GGACAUCUCG AUAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:189:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:189:
GGGAGAUAAG AAUAAACGCU CAAGAGCUCU UGACGAAAAC CUAUGCGAGA 50
AGGAUACUCG GUUUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:190:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:190:
GGGAGAUAAG AAUAAACGCU CAAGAGCUCU UGACGAAAAC CUACGCGAGA 50
UGGAAACUCG GUUUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:191:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 84 base pairs
(B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:191:

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GGGAGAUAAG AAUAAACGCU CAACACAGGG GUUUCAAACC UCCCCCUGAU      50
UCGGAGCUUC UUCGACAGGA GGCUCACAAC AGGC                       84
```

(2) INFORMATION FOR SEQ ID NO:192:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:192:

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GGGAGAUAAG AAUAAACGCU CAAAACCUCG CCAGGAAUAA CUUGCGACUU      50
UCGGAUCGUC UUAUUCGACA GGAGGCUCAC AACAGGC                    87
```

(2) INFORMATION FOR SEQ ID NO:193:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:193:

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GGGAGAUAAG AAUAAACGCU CAAGAGCUCU UGACGAAAAC CUAUGCGAGA      50
UGGAUACUCG GUUUUCGACA GGAGGCUCAC AACAGGC                    87
```

(2) INFORMATION FOR SEQ ID NO:194:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine

(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:194:

GGGAGAUAAG AAUAAACGCU CAACUUUGGA GCUCCUGGAA CGAAAGCGGA 50
AUUAACUUCC UUAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:195:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:195:

GGGAGAUAAG AAUAAACGCU CAAACAAUUC AGGACGGGGU UUCUUGAAUG 50
GGUUCGACCU UCAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:196:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:196:

GGGAGAUAAG AAUAAACGCU CAACCAGUAG AUCAACUCCC UGGCAACUGG 50
UUCGCCGUUA UAUUCGACAG GAGGCUCACA ACAGGC 86

(2) INFORMATION FOR SEQ ID NO:197:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:197:

GGGAGAUAAG AAUAAACGCU CAAACCUUGA UGUUCACUCC CUAACUCAAG 50

GUUCGACGUC UAUUCGACAG GAGGCUCACA ACAGGC 86

(2) INFORMATION FOR SEQ ID NO:198:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:198:

GGGAGAUAAG AAUAAACGCU CAAACAACCU GGACAAGGAA UUUUUCUAGU 50
GUUCGUUGGA CGUUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:199:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:199:

GGGAGAUAAG AAUAAACGCU CAAACCUUGA UGUUGAACUC CCUAACUCAA 50
GGCUCGACGU CUAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:200:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:200:

GGGAGAUAAG AAUAAACGCU CAAACGAAGG CAACUUCAAA CAUUUCCUUA 50
CGUUCCGCGC UCAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:201:
(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:201:

GGGAGAUAAG AAUAAACGCU CAAACGGCGC CAACAGCGAA UGUUCGCCCC 50
GUUCGGACGC UUAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:202:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:202:

GGGAGAUAAG AAUAAACGCU CAAACCGACA CAACCACGAC GUUCGGUCGG 50
UUUGUCCGAU UAUUCGACAG GAGGCUCACA ACAGGC 86

(2) INFORMATION FOR SEQ ID NO:203:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:203:

GGGAGAUAAG AAUAAACGCU CAAACGGAGG CAACCAAGAG AUUUCCAUCG 50
UUCGUUCGAU UGAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:204:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:204:

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GGGAGAUAAG AAUAAACGCU CAAUCCAUCC AACGCGGCAA GAUUUGAUGG 50
ACUUUGACGA UCAUUCGACA GGAGGCUCAC AACAGGC 87
```

(2) INFORMATION FOR SEQ ID NO:205:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:205:

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GGGAGAUAAG AAUAAACGCU CAAAAGCUCA GCAGAUCGGG ACUUCUGAUC 50
UUCGGGUCGC UUAUUCGACA GGAGGCUCAC AACAGGC 87
```

(2) INFORMATION FOR SEQ ID NO:206:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:206:

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GGGAGAUAAG AAUAAACGCU CAACAACGGU AGCGGCUAGA ACGCGCCGAC 50
UGAUUUAGGC UUAUUCGACA GGAGGCUCAC AACAGGC 87
```

(2) INFORMATION FOR SEQ ID NO:207:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:207:

GGGAGAUAAG AAUAAACGCU CAAUCCUCCU GUUCGGAGUC UCAAUGUCGA 50
CUCGGCCGGA CCUUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:208:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine

(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:208:

GGGAGAUAAG AAUAAACGCU CAAAGAAAUC CCCUUGAUUC GGAGUCGUCU 50
UUUCGAGCGU AGUUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:209:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine

(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:209:

GGGAGAUAAG AAUAAACGCU CAAAGAAAUC CCCUUGAUUC GGAGUCGUCU 50
UUUCGAGCGA AGGUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:210:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine

(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:210:

GGGAGAUAAG AAUAAACGCU CAAGAGAGUC AACUGCGAGA AUGGCUUUCC 50
CAACGGCACC UUUUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:211:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:211:
GGGAGAUAAG AAUAAACGCU CAAAGAUAAU CCCCCGGAUU CGGAGUCCUC 50
UUGACGAACU UCCUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:212:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:212:
GGGAGAUAAG AAUAAACGCU CAACGGAACA AACGGAAAUG GCACACAGGA 50
GAAAGACGAG ACCUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:213:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:213:
GGGAGAUAAG AAUAAACGCU CAACAGGAGA UUAAGGAACA GGCCACAGAU 50
AGAGACACGG AGCUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:214:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 85 base pairs
(B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:214:

GGGAGAUAAG AAUAAACGCU CAAAACUGGA CGAGAGGAGC UAGCGUCCAA 50
GUUCGGAGCU AUUCGACAGG AGGCUCACAA CAGGC 85

(2) INFORMATION FOR SEQ ID NO:215:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:215:

GGGAGAUAAG AAUAAACGCU CAAACUGAUU CUCAGCGGCU AGCGCUGAAG 50
UUCGACUAGU UCAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:216:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:216:

GGGAGAUAAG AAUAAACGCU CAAGGCCACA AGCAGAGAAC AGAACAACAG 50
AGCGAUGGAG AGAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:217:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine

(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:217:
GGGAGAUAAG AAUAAACGCU CAAGGAGCAU CCAGGAUAAC AGGCUAAACA 50
CCGCAAGGAC CAGUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:218:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:218:
GGGAGAUAAG AAUAAACGCU CAACGGAGGA AGGAAGAGGA ACCUUCGCCU 50
CUGAUUUAGC UUAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:219:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:219:
GGGAGAUAAG AAUAAACGCU CAACGUGGGC AAACUGAGGC AUUCCCCGCG 50
CUCAGAGAUU CAUUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:220:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:220:
GGGAGAUAAG AAUAAACGCU CAACAAUGGC AACUAGGCCA CAAAGUUCCC 50

ACUGAUUCGA CGUUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:221:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:221:
GGGAGAUAAG AAUAAACGCU CAAGCAAUCG GACCGAAAGG CCUUACCGAU 50
UUCUCGACCU UUCUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:222:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:222:
GGGAGAUAAG AAUAAACGCU CAACGGAGGA AGGAAGAGGA ACCUUUGCCU 50
CUGAUUUAGC UUAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:223:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:223:
GGGAGAUAAG AAUAAACGCU CAACGGAGGA AGGAAGAGGA ACCUUCGCCU 50
CUGAUUUAGC UUAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:224:
(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:224:

GGGAGAUAAG AAUAAACGCU CAAAGUCGAG UUUCAAGGAU CAUCCCCCUC 50
UUCGGAGCCU UUCUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:225:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:225:

GGGAGAUAAG AAUAAACGCU CAACGGAGGA AGGAAGAGGA GCCUUCGCCU 50
CUGAUUUAGC UUAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:226:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:226:

GGGAGAUAAG AAUAAACGCU CAACGAGGCC ACCGACAAGG AAGUCGACCG 50
GAGUUGAAGU AAAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:227:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:227:
GGGAGAUAAG AAUAAACGCU CAAGGCCCCU AGCGGGAUGC CGCUAAUCGC 50
GAAUCGAGGU UUAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:228:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:228:
GGGAGAUAAG AAUAAACGCU CAAUCGAUGC UAUCGAGUUC UACUCGGAAG 50
GUUCAACGUU UAAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:229:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:229:
GGGAGAUAAG AAUAAACGCU CAACCCAUAC UGAGAAAGAA CAGACUUCUC 50
AGGUUCGAAC GUUUCGACAG GAGGCUCACA ACAGGC 86

(2) INFORMATION FOR SEQ ID NO:230:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:230:

GGGAGAUAAG AAUAAACGCU CAACCUGAGA CGGUACGAGU UCGGACUCAG 50
GAUUUAACGC UUUUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:231:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: All C's are 2'-F cytosine

(ix) FEATURE:

(D) OTHER INFORMATION: All U's are 2'-F uracil

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:231:

GGGAGAUAAG AAUAAACGCU CAACUUACUC AACCUGCGAA CGCACAGGUU 50
AGUUCACCGU UUAUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:232:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: All C's are 2'-F cytosine

(ix) FEATURE:

(D) OTHER INFORMATION: All U's are 2'-F uracil

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:232:

GGGAGAUAAG AAUAAACGCU CAAACCCACA CUGAGAAAGA ACAGACUCCA 50
CAGGUUCGAA CGUUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:233:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: All C's are 2'-F cytosine

(ix) FEATURE:

(D) OTHER INFORMATION: All U's are 2'-F uracil

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:233:

GGGAGAUAAG AAUAAACGCU CAAAAACUCA UUCUGAGCUA AGCUCAAGUU 50
CUUGCAACGU UUGUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:234:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:234:

GGGAGAUAAG AAUAAACGCU CAAACCGAUU CUCGAAGCAG CACGCUCCAG 50
GUCUGACGUU UUUUCGACAG GAGGCUCACA ACAGGC 86

(2) INFORMATION FOR SEQ ID NO:235:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:235:

GGGAGAUAAG AAUAAACGCU CAAACCUAUA CUGAGAAAGA ACAGACUUCU 50
CAGGUUCGAA CGUUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:236:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:236:

GGGAGAUAAG AAUAAACGCU CAAAGGAACU UAUUCGACAU CAGUCGGUUC 50
CCUGGACGGG UUGUUCGACA GGAGGCUCAC AACAGGC 87

(2) INFORMATION FOR SEQ ID NO:237:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:237:

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GGGAGAUAAG AAUAAACGCU CAAGAACCUA UUCAACCGGA UUAGGUUGGU      50
UCUCGGAUGU CUAUUCGACA GGAGGCUCAC AACAGGC                    87
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(2) INFORMATION FOR SEQ ID NO:238:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 42 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:238:

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GACCUUCGUU UGACGCUCAU UCGACAGGAG GCUCACAACA GG              42
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(2) INFORMATION FOR SEQ ID NO:239:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 42 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:239:

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GACCUUCGUU UGACGCUUAU UCGACAGGAG GCUCACAACA GG              42
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(2) INFORMATION FOR SEQ ID NO:240:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:240:
CGUUCGGUCG GUUUGUCCGA UUAUUCGACA GGAGGCUCAC AACAGG 46

(2) INFORMATION FOR SEQ ID NO:241:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ix) FEATURE:
(D) OTHER INFORMATION: All C's are 2'-F cytosine
(ix) FEATURE:
(D) OTHER INFORMATION: All U's are 2'-F uracil
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:241:
GUCGUUUGUU CGACAGGAGG C 21

CLAIMS:

1. A method for identifying nucleic acid ligands and nucleic acid ligand sequences to a tissue target selected from the group consisting of peripheral blood mononuclear cells, fibrin clots, and carotid arteries comprising:

a) preparing a candidate mixture of nucleic acid sequences;

b) contacting said candidate mixture of nucleic acids with said tissue, wherein nucleic acids having an increased affinity to the tissue relative to the candidate mixture may be partitioned from the remainder of the candidate mixture;

c) partitioning the increased affinity nucleic acids from the remainder of the candidate mixture; and

d) amplifying the increased affinity nucleic acids to yield a mixture of nucleic acids enriched for nucleic acid sequences with relatively higher affinity and specificity for binding to said tissue, whereby nucleic acid ligands of said tissue may be identified.

2. The method of Claim 1 further comprising:

e) repeating steps b), c) and d).

3. The method of Claim 1 wherein said candidate mixture is comprised of single-stranded nucleic acids.

4. The method of Claim 3 wherein said single-stranded nucleic acids are ribonucleic acids.

5. The method of Claim 3 wherein said single-stranded nucleic acids are deoxyribonucleic acids.

6. A nucleic acid ligand to a tissue target identified according to the method of Claim 1.

7. A purified and isolated non-naturally occurring nucleic acid ligand to tissue target selected from the group consisting of peripheral blood mononuclear cells, fibrin clots, and carotid arteries.

8. The purified nucleic acid ligand of Claim 7 which is a non-naturally occurring nucleic acid ligand having a specific binding affinity for a tissue target molecule, such target molecule being a three dimensional chemical structure other than a polynucleotide that binds to said nucleic acid ligand through a mechanism which predominantly depends on Watson/Crick base pairing or triple helix binding, wherein said nucleic acid ligand is not a nucleic acid having the known physiological function of being bound by the target molecule.

9. The nucleic acid ligand of Claim 7 which is a deoxyribonucleic acid ligand.

10. The nucleic acid ligand of Claim 7 which is a ribonucleic acid ligand.

11. The nucleic acid ligand of Claim 7 wherein said target is a peripheral blood mononuclear cell.

12. The nucleic acid ligand to a peripheral blood mononuclear cell of Claim 11 wherein said ligand is a DNA ligand selected from the group consisting of the nucleotide sequences set forth in Table 2, or the corresponding RNA sequences thereof or the corresponding complementary sequences thereof.

13. The nucleic acid ligand of Claim 12 wherein said ligand is selected from the group consisting of SEQ ID NOS: 7-39.

14. A purified and isolated non-naturally occurring DNA ligand to a peripheral blood mononuclear cell, wherein said ligand is substantially

homologous to and has substantially the same ability to bind said peripheral blood mononuclear cell as a ligand selected from the group consisting of the sequences set forth in Table 2 or the corresponding RNA sequences thereof or the corresponding complimentary sequences thereof.

15. A purified and isolated non-naturally occurring DNA ligand to a peripheral blood mononuclear cell, wherein said ligand has substantially the same structure and the same ability to bind said peripheral blood mononuclear cell as a ligand selected from the group consisting of the sequences set forth in Table 2 or the corresponding RNA sequence thereof or the corresponding complementary sequences thereof.

16. The nucleic acid ligand of Claim 7 wherein said target is a fibrin clot.

17. The nucleic acid ligand to a fibrin clot of Claim 16 wherein said ligand is a RNA ligand selected from the group consisting of the nucleotide sequences set forth in Table 5, or the corresponding DNA sequences thereof or the corresponding complementary sequences thereof.

18. The nucleic acid ligand of Claim 17 wherein said ligand is selected from the group consisting of SEQ ID NOS: 43-130.

19. A purified and isolated non-naturally occurring RNA ligand to a fibrin clot, wherein said ligand is substantially homologous to and has substantially the same ability to bind said fibrin clot as a ligand selected from the group consisting of the sequences set forth in Table 5 or the corresponding DNA sequences thereof or the corresponding complimentary sequences thereof.

20. A purified and isolated non-naturally occurring RNA ligand to fibrin clot, wherein said ligand has substantially the same structure and the same

ability to bind said fibrin clot as a ligand selected from the group consisting of the sequences set forth in Table 5 or the corresponding DNA sequence thereof or the corresponding complementary sequences thereof.

21. The nucleic acid ligand of Claim 7 wherein said target is a carotid artery.

22. The nucleic acid ligand to a carotid artery of Claim 21 wherein said ligand is a RNA ligand selected from the group consisting of the nucleotide sequences set forth in Table 8, or the corresponding DNA sequences thereof or the corresponding complementary sequences thereof.

23. The nucleic acid ligand of Claim 22 wherein said ligand is selected from the group consisting of SEQ ID NOS: 141-237.

24. A purified and isolated non-naturally occurring RNA ligand to a carotid artery, wherein said ligand is substantially homologous to and has substantially the same ability to bind said carotid artery as a ligand selected from the group consisting of the sequences set forth in Table 8 or the corresponding DNA sequences thereof or the corresponding complimentary sequences thereof.

25. A purified and isolated non-naturally occurring RNA ligand to a carotid artery, wherein said ligand has substantially the same structure and the same ability to bind said carotid artery as a ligand selected from the group consisting of the sequences set forth in Table 8 or the corresponding DNA sequence thereof or the corresponding complementary sequences thereof.

Carotid SELEX-Schematic

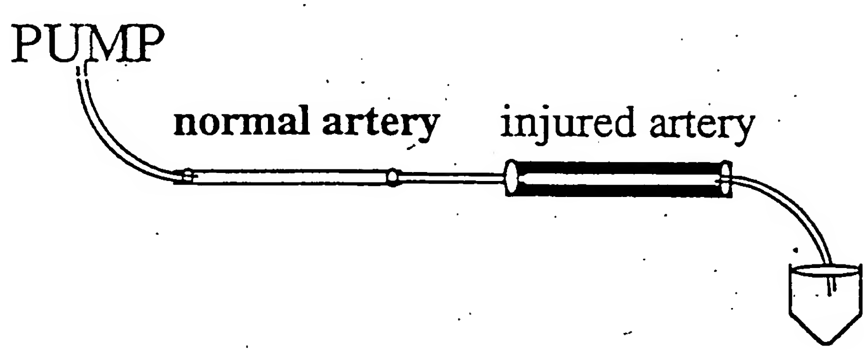

Figure 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/06059

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07H 21/02, 21/04; C12P 19/34; C12Q 1/68
US CL :435/6, 92.1; 536/22.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/6, 92.1; 536/22.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 92/14843 A1 (GILEAD SCIENCES, INC) 03 SEPTEMBER 1992, PAGES 29-31, 94-102.	1-20

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search 25 JULY 1996	Date of mailing of the international search report 27 AUG 1996
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer STEPHANIE W. ZITOMER, Ph.D. Telephone No. (703) 308-0196